

The University of Chicago.

Founded by JOHN D. ROCKEFELLER.

On the Hydrochlorides of Carbo-
phenylimido Derivatives.

A DISSERTATION

SUBMITTED TO THE FACULTIES OF THE GRADUATE SCHOOLS
OF ARTS, LITERATURE, AND SCIENCE, IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY.

By HERBERT N. McCOY.

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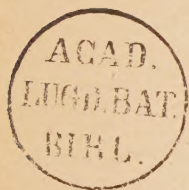
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On the Hydrochlorides of Carbo-phenylimido Derivatives.

HERBERT N. MCCOY.

Many bodies containing the carbo-phenylimido group, $C=NC_6H_5$, combine readily with acids, particularly the halogen acids, to form salt-like compounds. In the preceding paper by Prof. Stieglitz, it is shown that it is a question of considerable importance to determine experimentally whether, in any given class of such compounds, the acid is taken up by the nitrogen atom, forming ammonium derivatives; or is absorbed by the double bond between carbon and nitrogen, the halogen going to the carbon and the hydrogen to the nitrogen atoms, while the valence of the nitrogen remains unchanged.

The work, an account of which is given in the present paper, was undertaken at the suggestion and under the direction of Dr. Stieglitz, with the object of investigating two such cases. The first part of the paper deals with the experiments on the constitution of the hydrochlorides, etc., of phenylimido acid esters, $RC(:NR)OR$; the second part comprises a study of the constitution of the addition-products of hydrogen chloride and carbodiphenylimide, $C(:NC_6H_5)_2$.

PART I.

On the Hydrochlorides of Phenylimido Acid Esters.

The imido esters, $R''C(:NR)OR'$, form crystalline salts with acids¹, particularly with the halogen acids. These salts have been considered by their discoverer, Pinner, and by

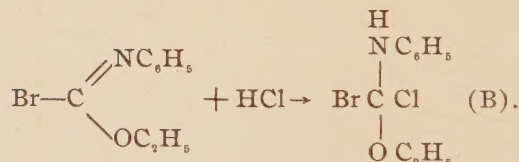
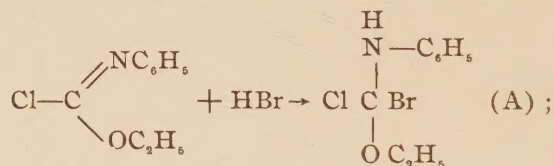
¹ Pinner: Ber. d. chem. Ges., 10, 11, 16, 17, etc.

others, to have the general constitution, (I) $R''C(OR')-(\text{:N}^{\vee}RHX)$, the nitrogen atom being quinivalent.

In 1894 Lengfeld and Stieglitz¹ in the course of a study of the action of phosphorus pentachloride on phenylurethane, were led to examine the question whether the salts of the imido esters might not have the constitution represented by

the formula, (II) $R''C \begin{array}{l} \text{H} \\ \diagup \text{NR} \\ \diagdown \text{OR}' \end{array} \text{X}$, the hydrogen haloid having been

added to the double bond. The results of their investigation of the action of hydrogen bromide on ethyl phenylimidochlorformate and of hydrogen chloride on ethyl phenylimidobromformate indicated that in both cases the same addition-product or salt is formed. This is only possible if formula II represents the true constitution of these salts.

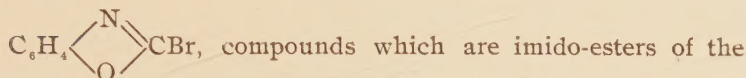
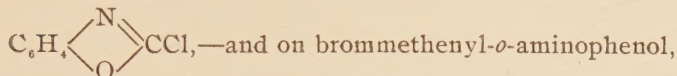


The products A and B should be identical. The identity of these salts could not be proved by isolating them, as they decompose below -15° . However, as A and B gave the same *decomposition-products* (in both cases chiefly ethyl bromide and chlorformanilide) the only simple explanation is to be found in the assumption that the above identical addition-compounds are the intermediate products of the reaction.

The fact that the salts mentioned were too unstable to be

¹ This JOURNAL; 16, 70; 17, 98.

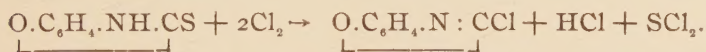
isolated and compared directly made it desirable to obtain and compare more stable salts of the same class of compounds. With this object in view, I have investigated the salts formed by the action of acids on chlormethenyl-*o*-aminophenol¹,



same type as the compound $\text{R}''\text{C}(:\text{NC}_6\text{H}_5)\text{OR}$.

A great deal of work was necessary in order to find suitable methods for preparing the substances.

Chlormethenylaminophenol (carbonylaminophenol chloride) had been prepared by Seidel² by the action of phosphorus pentachloride on *o*-thiocarbamidophenol; but the yield was poor, and the method failed entirely, in attempting to prepare the brommethenylaminophenol, necessary for the investigation, by the action of phosphorus pentabromide on the thio-compound. After trying a number of methods described below, it was found that these two substances can be prepared very readily and with excellent yields by the action of dry chlorine or bromine on the thio-compound suspended in dry chloroform, and subsequent treatment with water, thus :



On account of the ring structure of these imido esters the hydrogen-haloid addition-products should show no tendency to split off aliphyl haloid, corresponding to a loss of ethyl haloid in the case of the bodies studied by Lengfeld and Stieglitz; in fact, the addition-products were found to be capable of isolation.

The hydrochloride, obtained by the action of dry hydrogen chloride on a ligroin solution of chlormethenylaminophenol is a white crystalline salt-like body, which is stable in an atmos-

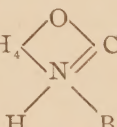
¹ Concerning the nomenclature *vide* Ladenburg : Ber. d. chem. Ges., 10, 1124.

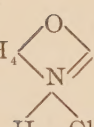
² J. prakt. Chem., [2], 42, 454.

phere of hydrogen chloride at the ordinary temperature, and decomposes, with loss of hydrogen chloride, at 57° . Water dissociates the salt at once into hydrochloric acid and chlormethenylaminophenol; but in concentrated hydrochloric acid chlormethenylaminophenol, which is an oil insoluble in water, is very readily soluble and separates as the unchanged oil, on diluting with water; thus showing that the oil is a true, though weak base.

The hydrobromide of chlormethenylaminophenol, obtained by the action of carefully dried hydrogen bromide on a solution of the chlorine compound in dry ligroin, was found to be a fairly stable substance, decomposing, when dry, only above 155° .

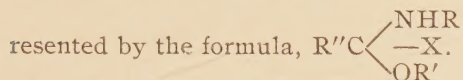
The hydrochloride of the corresponding brommethenylaminophenol, prepared from the latter by the addition of dry hydrogen chloride, had the same composition, melting-point and other properties as the above hydrobromide of chlormethenylaminophenol. The salts are decomposed by water, *both giving hydrobromic acid and chlormethenylaminophenol*. The two bodies appear to be identical in every respect. This can only be the case when both bodies are represented by the formula, $\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CClBr}$; while according to the old concep-

tion the bodies would have the formulas, C_6H_4  and

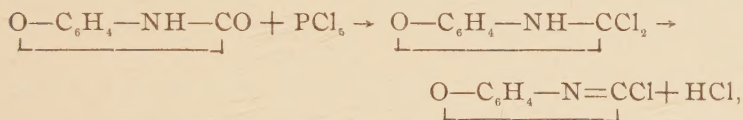
C_6H_4  CBr , and they would evidently have different prop-

erties. Besides those mentioned, other salts of these substances were prepared and analyzed: the nitrate, and the chlorplatinate of chlormethenylaminophenol, and the hydrobromide of brommethenylaminophenol, thus establishing their salt-like nature beyond a doubt.

The results of the investigation of the salts of chlor- and of brommethenylaminophenol are therefore in complete accord with the views of Lengfeld and Stieglitz¹ on the constitution of the salts of the amido ethers. Carbo-phenylamido derivatives are weak bases and the hydrogen-haloid addition-products are true salts, in which *the halogen is bound to carbon* and the hydrogen to nitrogen; and they may in general be represented by the formula,



In connection with the investigation of the salts of chlor-methenylaminophenol, the opportunity was used to study the action of phosphorus pentachloride on carbonylaminophenol somewhat more fully than had been done by previous investigators.² It was decided to determine whether carbonylaminophenol or certain of its derivatives would react with phosphorus pentachloride according to:



with the object, not only of finding a convenient method for preparing the halogen methenylaminophenols used in this work; but more particularly of getting more evidence on the action of phosphorus pentachloride on urethanes, which action was supposed to take place according to the equation just given.³ The results obtained were in accord with those of Bender and of Chelmiki. Chlormethenylaminophenols could in no case be obtained (except perhaps in traces) by the action of phosphorus pentachloride on any of the derivatives of carbonylaminophenols. While, as a method of preparation, the experiments have proved unsuccessful, they show, in connection with the results of Bender and Chelmiki, that the action of phosphorus pentachloride on urethanes does not take place according to the above equation.

¹ *Loc. cit.*, and Stieglitz: This JOURNAL, 21, 101.

² Bender: Ber. d. chem. Ges., 19, 2271; Chelmiki: *Ibid.*, 20, 178.

³ Lengfeld and Stieglitz: This JOURNAL, 16, 72.

EXPERIMENTAL PART.

The Action of Potassium Hypobromite on Salicylic Amide.

In order to prepare the carbonylaminophenol needed, a new method was tried, starting from salicylic amide, and based on the molecular rearrangement which bromamides show when treated with alkalies or alcoholic sodium methylate¹.

The preparation of salicylic amide by heating the methyl ester with concentrated aqueous ammonia² gives good results only when the heating is continued several days at 100°. By heating, in a sealed tube, one part of the ester with two parts of 36 per cent. ammonia and one and one-half parts of pure methyl alcohol for six hours at 100°, very good yields of the amide were obtained. The alcohol greatly accelerates the action by dissolving both the ester and the ammonia. From theoretical considerations, it is evident that the ultimate yield of amide must be somewhat diminished by the use of alcohol; but the cheapness of the material, the greater purity of the product, and the saving of time make the new method preferable.

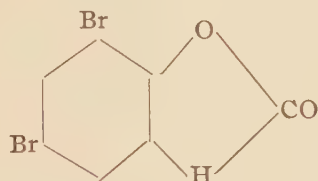
To prepare salicylic bromamide the method of Hoogewerff and Van Dorp³ was adopted. To an alkaline solution of potassium hypobromite, made from one molecule of bromine and four molecules of caustic potash in 10 per cent. solution, was added one molecule (5 grams) of dry salicylic amide in small portions, the temperature of the solution being kept below 5°. The amide dissolved forming a clear solution, which, treated with cold dilute acetic acid, gave a nearly white precipitate. This was not the expected salicylic bromamide, since, when treated with potassium iodide and hydrochloric acid, no iodine was liberated. Further examination showed the precipitate to consist of a body containing bromine mixed with much unchanged salicylic amide. A second experiment, with two molecules of bromine and six of caustic potash to one of the amide, gave a similar product which, however, contained less unchanged amide. Finally, one molecule of salicylic amide

¹ Hofmann; Ber. d. chem. Ges., **15**, 762; Hoogewerff and Van Dorp: Recueil trav. chim., **9**, 33; **10**, 4; Lengfeld and Stieglitz: This JOURNAL, **15**, 215, 504; **16**, 370.

² Spilker: Ber. d. chem. Ges., **22**, 2768.

³ Rec. trav. Chim., **4**, 373.

(5 grams) was added to the alkaline hypobromite solution, obtained from three molecules of bromine (17.8 grams) and eight molecules of caustic potash (16.5 grams) in 150 cc. of water. This reaction like the two preceding was carried out below 5°. The nearly white precipitate, obtained with cold dilute acetic acid, did not react with potassium iodide; thus showing the absence of bromamide. From hot glacial acetic acid the body crystallizes on cooling in spherical aggregates of almost colorless needles melting at 243°–247°. Very slight decomposition seems to take place on boiling with acetic acid. After several recrystallizations from benzene, in which the body is but slightly soluble, the substance is pure white, and melts at 250°. The new body was proved to be 3-5-dibromcarbonylaminophenol,



by its analysis, by its reduction to carbonylaminophenol, and by its synthesis from 3-5-dibromsalicylic amide.

0.3790 gram gave 17.5 cc. N₂ at 23.5° and 738.6 mm.

	Calculated for C ₇ H ₃ Br ₂ NO ₂ .	Found.
N	4.79	5.07

Jakoby¹ has made a dibromcarbonylaminophenol (m. p. 243°–245°), by the action of bromine water on a water solution of carbonylaminophenol. When a sample of the substance, prepared according to Jakoby, was compared with the above substance the two were found to have quite similar properties, but that they were not identical was shown by the melting-point (about 210°) of a mixture of the two; each substance, separately, melts 35–40° higher. The reduction of both of the above bodies to carbonylaminophenol is readily accomplished.

¹ J. prakt. Chem., [2] 37, 51.

Reduction of Dibromcarbonylaminophenol.—0.2 gram of Jakoby's dibrom body was shaken thirty minutes with 10 grams of $2\frac{1}{2}$ per cent. sodium amalgam and 25 cc. of water; the body, being readily soluble in alkali, soon dissolved. After filtering from mercury and acidifying, the white precipitate formed was crystallized from hot water. It formed colorless needles, free from bromine, melting at 138° , and having all the properties of carbonylaminophenol; by mixing with pure carbonylaminophenol, the melting-point remained unchanged.

One gram of the dibrom body from salicylic amide was reduced by sodium amalgam as above. The precipitate with acid was free from bromine; from hot water it crystallized in colorless needles, which melt at 138° . The properties of the substance are those of carbonylaminophenol; its complete identity with this body was established by the melting-point, 138° , of their mixture. The last experiment furnishes conclusive proof that the dibrom body obtained by the action of hypobromite on salicylic amide is a dibrom derivative of carbonylaminophenol.

The isomerism of the body obtained from salicylic amide, with that obtained by brominating carbonylaminophenol directly, pointed to a bromination of the aromatic ring as the first step of the reaction of hypobromite on salicylic amide.

Synthesis of 3-5-Dibromcarbonylaminophenol. — Salicylic amide reacts with aqueous bromine with the greatest ease, forming 3-5-dibromsalicylic amide.¹ To a solution of 10 grams of 3-5-dibromsalicylic amide, made according to Spilker, and 4 grams (2 molecules) of caustic potash in 180 cc. of water, cooled to 0° , was added slowly an ice-cold solution of hypobromite resulting from 5.4 grams (1 molecule) of bromine and 5 grams ($2\frac{1}{2}$ molecules) of caustic potash in 60 cc. of water. A white crystalline mass resulted. The crystals, which were evidently the potassium salt² of the dibromcarbonylaminophenol, were filtered from a slightly colored mother-liquor; dissolved in 250 cc. of water, and an excess of dilute acetic acid added. The white amorphous precipitate formed was filtered off; washed with water, in which it is

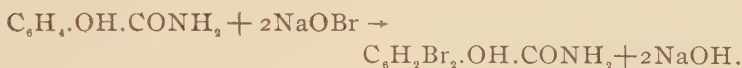
¹ Spilker; Ber. d. chem. Ges., **22**, 2769. ² Vide, p. 19

nearly insoluble ; and dried on a clay plate. The yield was 6.7 grams. After recrystallization from hot benzene the substance was perfectly pure. It had the melting-point, 250° , and all the properties of the body obtained by the action of 3 molecules of hypobromite on salicylic amide ; by mixing with the latter, the melting-point remained unchanged. A bromine determination confirmed the identity.

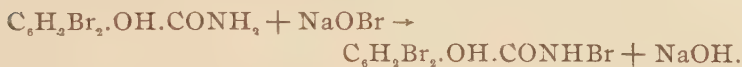
0.1303 gram heated with lime gave 0.1674 gram AgBr.

	Calculated for $C_7H_3Br_2NO_2$.	Found.
Br	54.61	54.80

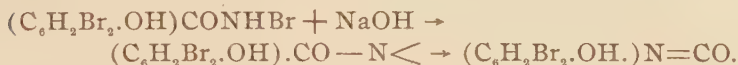
The first product of the action of hypobromite on salicylic amide is, therefore, 3-5-dibromsalicylic amide :



This, by the action of another molecule of hypobromite, must give 3-5-dibromsalicylic bromamide :



The bromamide undergoes rearrangement so rapidly that it at once gives the isocyanate :¹



The latter reacts immediately with the neighboring phenol-hydroxyl group to give the product obtained :



The great ease with which dibromsalicylic bromamide is rearranged is remarkable. In no other case has such a rearrangement taken place so rapidly, that the bromamide could not be isolated.

Aside from the ease with which the process takes place, the whole series of reactions is perfectly normal.

Salts of Dibromcarbonylaminophenols.—Both dibromcarbonylaminophenols form salts with alkalies. The potassium salt of Jakoby's body was obtained as well-formed white

¹ Stieglitz : This JOURNAL, 18, 75.

needles, by the addition of an excess of 30 per cent. caustic potash to a clear solution of the dibrom body dissolved in a little dilute solution of caustic potash. The salt was purified by dissolving it in acetone, in which it is readily soluble, and adding ligroin (boiling-point 60° – 70°), when the salt separated in beautiful white needles, which decompose above 300° . The analysis was made by dissolving the salt in water, adding $\frac{N}{10}$ -hydrochloric acid in slight excess, and titrating back with $\frac{N}{10}$ -potassium hydroxide using methyl orange. The dibrom body was precipitated by the acid, but was not filtered off, as it does not affect the indicator.

0.4739 gram required 14.6 cc. $\frac{N}{10}$ -HCl; calculated for $C_7H_2Br_2NO_2K$, 14.3 cc.

The sodium salt, white needles, was prepared similarly.

0.7525 gram required 24.2 cc. $\frac{N}{10}$ -HCl; calculated for $C_7H_2Br_2NO_2Na$, 23.9 cc.

The salts of 3-5-dibromcarbonylaminophenol resemble the above salts, but are more soluble in water and acetone.

The Action of Phosphorus Pentachloride on Dibromcarbonylaminophenol.—Attempts¹ to obtain chormethenylaminophenol by the action of phosphorus pentachloride on carbonylaminophenol have led to a mixture of bodies chlorinated in the ring. The action of phosphorus pentachloride on Jakoby's dibromcarbonylaminophenol was tried with the hope that, owing to the protection afforded by the halogen already in the ring, a chlormethenyldibromaminophenol would result, by a smooth reaction. It was found that phosphorus pentachloride does not act on the dibrom body when the two are heated with dry, boiling chloroform, in which the dibrom body is somewhat soluble; neither do the dry substances react when heated all day in a sealed tube at 100° . At 200° a reaction took place; the tube contained hydrochloric acid, and the black residue had the odor of phosphorus oxychloride. About one-third of the material used was recovered unchanged, but no other pure substance could be isolated.

¹ Bender: Ber. d. chem. Ges., **19**, 2271; Chelmiki: *Ibid*, **20**, 178.

The Action of Phosphorus Pentachloride on the Sodium Salt of Carbonylaminophenol.

Carbonylaminophenol was prepared according to Bender's¹ method, from his so-called ethyl aminophenylcarbonate, $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OCOOC}_2\text{H}_5$. The latter was made from ethyl *o*-nitrophenylcarbonate. Instead of using an alcoholic solution of potassium nitrophenol, I treated the aqueous solution of the potassium salt with chlorcarbonic ether and obtained quantitative yields of ethyl nitrophenylcarbonate, which I found distills with no apparent decomposition at $176^\circ-178^\circ$ under 21 mm. pressure. It was found too that alcohol could be omitted with advantage, in the reduction which is readily accomplished when concentrated hydrochloric acid is added in small portions to a mixture of tin and the ester, the flask being cooled to prevent much rise of temperature. After diluting the solution of the reduced substance with an equal volume of water, and filtering from the remaining tin and sediment, a perfectly clear and colorless solution is obtained. This solution may be kept several hours without showing signs of crystallization, but slowly deposits pure white crystals on prolonged standing. If, however, the clear solution is heated to 90° for 10 minutes, it becomes very turbid with oily drops, and on cooling the whole of the reduction product separates *at once* in the form of white crystals. The latter are now insoluble in dilute acids, but dissolve readily in alkalies. In spite of the fact that the body is an *acid* and *not a base*, Bender described it as aminophenylethyl carbonate, $\text{NH}_2-\text{C}_6\text{H}_4-\text{OCOOC}_2\text{H}_5$, which no doubt exists at first in the acid solution obtained in the reduction. Mr. J. H. Ransom² working in this laboratory, on this subject with Dr. Stieglitz has now proved that a rearrangement takes place in the acid solution leading to the formation of oxyphenylurethane, $\text{C}_2\text{H}_5\text{O}_2\text{CNHC}_6\text{H}_4\text{OH}$ or $\text{NH}-\text{C}_6\text{H}_4-\text{O}-\text{C}(\text{OH})\text{OC}_2\text{H}_5$.

The results of this investigation will be published at a later date in this Journal.

¹ Ber. d. chem. Ges., 19, 2269.

² *Ibid.*, 31, 1055.

By heating the above urethane to 230° it was converted into carbonylaminophenol, with loss of alcohol.

Upon mixing a concentrated solution of carbonylaminophenol in absolute alcohol with the calculated amount of alcoholic sodium ethylate, a gray crystalline precipitate of the sodium salt is formed, the amount of which is increased by the addition of ligroin. The salt is very easily soluble in water and in alcohol; with dilute acids, even carbonic acid, carbonylaminophenol is regenerated.

The dry sodium salt was treated with phosphorus pentachloride, under various conditions, with the hope of obtaining chlormethenylaminophenol. The reaction was always complicated, giving a mixture of products from which very little and often none of the desired body could be isolated. It was thought possible that ethoxymethenylaminophenol, $\text{O}-\text{C}_6\text{H}_4-\text{N}=\text{C}-\text{OC}_2\text{H}_5$, might be converted into chlor-

methenylaminophenol by the action of phosphorus pentachloride. This ester has been made from *o*-aminophenol and imido-carbonic ester¹; but for this experiment it was prepared by the action of alcohol and sodic hydrate on chlormethenylaminophenol, which latter is readily obtained in another way (see below). The body thus made had the boiling-point and other properties ascribed to it by Sandmeyer. By heating with aqueous hydrochloric acid it was readily split into carbonylaminophenol and ethyl chloride. The ester reacts with phosphorus pentachloride only on heating, but no chlormethenylaminophenol was found in the resulting product.

The experiments just described prove that it is impossible to replace the carbonyl oxygen in carbonylaminophenol by halogen by any possible variation of the conditions. They show that it is extremely unlikely, that the action of phosphorus pentachloride on any urethane takes place according to the equation:



As these methods failed to lead to chlor- and brommethenylaminophenols, I returned to Seidel's method for the preparation of the former body; *viz.*, by the action of phosphorus

¹ Sandmeyer: Ber. d. chem. Ges., 19, 2655.

pentachloride on thiocarbamidophenol. In this reaction, besides the body desired, other products containing chlorine and phosphorus were also obtained, as has already been observed by Seidel. The separation of pure chlormethenylaminophenol from these by-products and the phosphorus sulphochloride formed is very troublesome, and the yield is usually poor; while with phosphorus pentabromide not a trace of the corresponding brommethenylaminophenol was obtained.

The chlorinating effect of phosphorus pentachloride made it seem probable, that, in Seidel's reaction, the formation of chlormethenylaminophenol was chiefly due to the action on the thio body of chlorine, liberated from phosphorus pentachloride at the temperature used. If this were true, by using chlorine alone, under the most favorable conditions, a much smoother reaction should occur.

As a precedent, the case of phenyl mustard-oil may be mentioned; when heated with phosphorus pentachloride¹ this gives a mixture of phenylimidocarbonyl chloride, chlormethenylaminothiophenol and other chlorinated products; while, by the action of chlorine² *in the cold*, Nef³ has obtained only phenylimidocarbonyl chloride, in almost quantitative yield:



The following reaction shows the correctness of the above assumption.

The Action of Chlorine on o-Thiocarbaminophenol:—Chormethenylaminophenol, O—C₆H₄—N=CCl.

Ten grams of finely powdered and carefully dried *o*-thiocarbaminophenol, made according to Dünner,⁴ was suspended in 100 grams of perfectly dry chloroform free from alcohol, in which the thio-body is not very soluble; and carefully dried chlorine slowly passed into the mixture. The flask was cooled with water to prevent a rise of temperature above 20°. The chlorine is readily absorbed at first, and the stream is continued until absorption no longer takes place. The chloroform solution, in which the reaction-products are easily solu-

¹ Hofmann : Ber. d. chem. Ges., **12**, 1127.

² Sell and Zierold : *Ibid.*, **7**, 1228.

³ Ann. Chem. (Liebig), **270**, 284.

⁴ Ber. d. chem. Ges., **9**, 465.

ble, is poured slowly, with vigorous shaking, into half a liter of cold water, in order to decompose the sulphur dichloride formed. After washing with dilute caustic soda and water, until no odor of chlorine or sulphur chloride remained, the chloroform solution was dried with calcium chloride and distilled. 9.2 grams of nearly colorless oil resulted, which, on redistillation gave 8.5 grams of a pure colorless oil, boiling at 200° . The substance has the boiling-point, the odor, and other properties of chlormethenylaminophenol, obtained by the action of phosphorus pentachloride on thiocarbaminophenol. With aqueous hydrochloric acid it is readily decomposed, giving carbonylaminophenol (m. p. 138°). Its index of refraction, as determined with the Abbey refractometer, at 20° , is 1.5678.



As has already been stated, the action of phosphorus pentabromide on thiocarbaminophenol does not give the above bromide; neither is the chlorine in chlormethenylaminophenol replaced by bromine by treating the chlor body with an excess of bromine. Attempts to prepare the bromide by a method similar to that by which the chloride was obtained (*viz.*, by the direct action of halogen on thiocarbaminophenol) were not at first successful.

According to the equation,



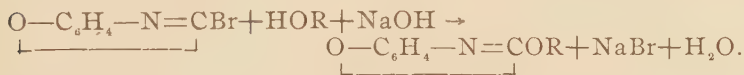
two molecules of bromine are required for each molecule of the thio-body; and this was the amount used in the first experiments which proved unsuccessful. Only when much more bromine (7 to 8 atoms) is used can the bromide be obtained. 38 grams of bromine, in 50 grams of pure *dry* chloroform, were added very slowly, with constant shaking, to 10 grams of thiocarbaminophenol, suspended in 75 grams of pure dry chloroform. At first a heavy brick-red precipitate is formed; but, with an excess of bromine this changes to a heavy, insoluble, dark oil. After adding the bromine, which requires perhaps three-quarters of an hour, the mixture is

allowed to stand a short time ; then treated with water and sodic hydrate, as in the preparation of chlormethenylaminophenol. The treatment with water causes the insoluble oil to become soluble in chloroform ; the latter, after drying with calcium chloride, was distilled off, leaving an oily residue. This oily residue, consisting chiefly of brommethenylaminophenol, was treated with ligroin (b. p. 40–60°), which dissolves the brom-body leaving a small, dark residue. Its purification is best accomplished by passing into the ligroin solution pure dry hydrogen bromide, which precipitates the hydrobromide of brommethenylaminophenol. This is filtered off and treated with much water, which causes an immediate decomposition into hydrobromic acid and brommethenylaminophenol ; the latter is again taken up in ligroin, and the dried ligroin solution again precipitated with hydrogen bromide. After repeating the precipitation and treatment with water several times, the dried ligroin solution was evaporated in a vacuum, and the last traces of ligroin removed in a current of dry air, in the presence of potassium hydroxide and paraffin. On cooling with ice-water, white crystals were obtained, melting at 27°. These were brommethenylaminophenol as the following analysis shows :

0.2838 gram required 14.2 cc. $\frac{N}{10}$ AgNO₃.

	Calculated for C ₇ H ₄ BrNO.	Found.
Br	40.40	40.03

The analysis was made by treating the substance with alcohol and dilute sodic hydrate, when the following reaction¹ takes place :



The solution was acidulated with nitric acid and titrated according to Volhard.

Chlormethenylaminophenol Hydrochloride:—*Dichlorcarbonylaminophenol*, $\text{O} - \text{C}_6\text{H}_4 - \text{NH} - \text{CCl}_2$.
└──────────┘

Carefully dried hydrogen chloride is passed into 0.5 gram of

¹ *Vide*, p. 12

chlormethenylaminophenol dissolved in 8 cc. of dry low-boiling ligroin, in a well-stoppered vessel, provided with an exit tube. Beautiful white crystals are soon deposited on the walls of the vessel. When the quantity of crystals no longer increases, the liquid is poured off completely and 4-5 cc. of fresh ligroin added, and again decanted. The latter operation is accomplished as quickly as possible to avoid absorption of moisture from the air. The crystals are then freed from ligroin in a current of dry hydrogen chloride, a pump being used to secure a partial vacuum. In a short time the ligroin has evaporated, but a portion of the hydrochloride has decomposed into its constituents. More hydrogen chloride is then passed in until the crystals appear free from oil. The new substance is the very unstable hydrochloride of chlormethenylaminophenol. It is stable only in an atmosphere of dry hydrogen chloride at very nearly atmospheric pressure. It decomposes into its constituents very rapidly in a vacuum, or in dry air, where the partial pressure of hydrogen chloride is also zero. As might be expected it is instantly decomposed by water. A small amount of the hydrochloride, made in a small test-tube, was heated in a water-bath, while a current of dry hydrogen chloride was passed through the tube. Under these conditions the substance melts with decomposition at 57° - 58° (thermometer in bath).

The analysis of such an unstable compound cannot, of course, be made by ordinary methods, but was accomplished by quickly bringing the freshly prepared crystals upon a watch-glass, moving this through the air *3 or 4 seconds* to free them from adhering hydrogen chloride, and *immediately* pouring the substance into a tared, wide-mouthed weighing-bottle, containing 25 to 30 cc. of water, and weighing again. The crystals are decomposed at once into hydrochloric acid and chlormethenylaminophenol, which settles to the bottom as a colorless oil. Methyl orange was added and the solution titrated with $\frac{N}{10}$ -alkali. In neutral or alkaline solution chlormethenylaminophenol is attacked only very slowly by water. In concentrated acid solution, however, it is soluble, and the decomposition by water goes on quite rapidly; but, at the di-

lution used in the analysis, the decomposition is inappreciable.

Substance.	Calculated for $C_7H_5NOCl_2$ (one mol. of acid) cc. tenth- normal alkali.	Found.
Gram.		cc.
O.1720	9.05	8.65
O.1024	5.39	5.24

Considering the great instability of the body, these figures are as good as could be expected.

Chlormethenylaminophenol Hydrobromide :—*Chlorbromcarbonylaminophenol*, $O-C_6H_4-NH-CClBr$.

One gram of chlormethenylaminophenol was dissolved in 40 cc. of low-boiling ligroin and treated with dry hydrogen bromide. The hydrobromide of chlormethenylaminophenol appears immediately as a white precipitate, which is much more stable than the hydrochloride. The precipitate was quickly filtered off with a pump, pressed on a clay plate a few moments, and dried in a vacuum over potassium hydroxide for about five minutes. The analysis was made as in the case of the dichloride.

	Substance.	Calculated for $C_7H_5NOClBr$ (one mol. of acid) cc. tenth- normal alkali.	Found.
	Gram.		cc.
I.	0.3420	14.58	14.35
II.	0.1590	6.78	6.86

The substance is a white powder, which melts at 155° with decomposition. It quickly loses one molecule of acid in contact with water.

The neutralized solution, in analysis II. above, was separated from the insoluble oil and precipitated with silver nitrate. A weighed portion of the dried silver haloid was reduced to metallic silver.

I. 0.1193 gram of the dry silver salt gave 0.0693 gram Ag.

A second preparation of silver haloid was made from the solution resulting from the action of water on another sample of freshly prepared hydrobromide.

II. 0.2220 gram of the dry silver salt gave 0.1304 gram Ag.

	Calculated for AgCl.	Calculated for AgBr.	Found. I.	Found. II.
Halogen	24.73	42.55	41.91	41.26

The result shows that, by the action of water on chlormethenylaminophenol hydrobromide, hydrobromic acid is split off almost without any hydrochloric acid.

Brommethenylaminophenol Hydrobromide:—*Dibromcarbonylaminophenol*, $\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CBr}_2$.

By passing dry hydrogen bromide into a ligroin solution of brommethenylaminophenol, the hydrobromide is obtained as an almost colorless precipitate. It was dried and analyzed exactly as was the hydrobromide of chlormethenylaminophenol. The new salt melts with decomposition at 163° , and is decomposed by contact with water.

Substance.	Calculated for $\text{C}_7\text{H}_5\text{NOBr}_2$ (one mol. of acid) cc. tenth- normal alkali.	Found.
Gram.		cc.
0.1451	5.20	5.31

Brommethenylaminophenol Hydrochloride:—*Chlorbromcarbonylaminophenol*, $\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CBrCl}$.

A ligroin solution of brommethenylaminophenol was precipitated by dry hydrogen chloride. The nearly white precipitate resembles the hydrobromide of chlormethenylaminophenol in every respect, except in having a slight tinge of color, due to the fact that perfectly pure and colorless brommethenylaminophenol was not used, on account of the difficulty of preparing it. The new salt melts, with decomposition, at 155° , which is also the melting-point of the hydrobromide of the chlor-body. The melting-point of a mixture of the two freshly-prepared salts is also 155° . The new body is decomposed at once by water, *hydrobromic acid being chiefly split off*, with only traces of hydrochloric acid.

	Substance.	Calculated for $\text{C}_7\text{H}_5\text{NOBrCl}$ (one mol. of acid) cc. tenth- normal alkali.	Found.
	Gram.		cc.
I.	0.3414	14.56	12.83
II.	0.2580	11.00	10.68
III.	0.2279	9.72	9.42

The filtrate from analysis I. was precipitated by silver nitrate and a portion of the silver halide reduced to silver.

I. 0.2195 gram of the dry silver salt gave 0.1301 gram Ag. Another filtrate from some freshly prepared hydrochloride of the brom-body treated with water, was precipitated with silver nitrate.

II. 0.3967 gram of the dry silver salt gave 0.2299 gram Ag.

	Calculated for AgCl.	Calculated for AgBr.	Found. I.	Found. II.
Halogen	24.73	42.55	40.73	42.05

As evidence of the identity of the hydrobromide of chlor-methenylaminophenol and the hydrochloride of brommethenylaminophenol we have the agreement in physical properties and melting-point and the fact that their mixture melts at the same temperature; but, since the bodies melt with some decomposition, it does not necessarily follow that their identity is absolutely proved by this latter fact as would be the case with bodies that melt without decomposition. However, the behavior with water, by which both split off chiefly hydrobromic acid with only traces of hydrochloric acid, is a fact which is inexplicable on any ground except the identity of the two bodies. The identity of these bodies justifies, therefore, the constitutions already ascribed to them; all of the halogen is consequently attached to carbon. That, moreover, these bodies are true salts was shown by the preparation of other salts and by obtaining ionic reactions in aqueous solutions.

Chlormethenylaminophenol Nitrate, $\text{O}_2\text{C}_6\text{H}_4\text{—NH.C.Cl.ONO}_2$.

Seidel states¹ that with concentrated nitric and hydrochloric acids chlormethenylaminophenol gives beautiful crystalline salts; but he does not give analyses nor further data, proving that these are really salts of chlormethenylaminophenol. The nitrate is readily obtained by treating the oil (0.3 to 0.4 gram) with 10 cc. of nitric acid (sp. gr. 1.28) at 0°. The oil dissolves and white crystals separate at once. These were quickly drained on a platinum cone with the aid of a pump,

¹ J. prakt. Chem. [2], 42, 455.

rubbed on a clay plate for a minute or two, and then dried over sulphuric acid in a vacuum, for 30 to 40 minutes. If the nitric acid is too concentrated or is allowed to remain in contact with the crystals too long, or if the temperature is allowed to rise much above 0° the salt becomes yellow, apparently on account of nitrification. The nitrate forms beautiful white crystals, which become yellow and finally brown on being kept a few hours in a desiccator. In contact with water the salt suffers complete hydrolysis into chlormethenylaminophenol and nitric acid. The analysis was made by bringing the dried crystals into a large, tared, wide-mouthed weighing-bottle, weighing quickly, then adding water and a drop of methyl orange and titrating with $\frac{N}{10}$ -alkali.

	Substance. Gram.	Calculated for $C_6H_4ClNO.HNO_3$. cc. tenth-normal alkali.	Found. cc.
I.	0.2592	12.0	11.8
II.	0.3974	18.4	19.0

The substance used in analysis II. had become slightly yellow; that in I. was pure white. A test of the solutions, after titrating in the above analysis, showed only traces of chlorine.

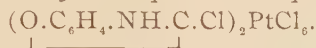
The Action of Hydrochloric Acid on Chlormethenylaminophenol.

When chlormethenylaminophenol is treated with cold concentrated hydrochloric acid it dissolves very readily and the oil separates out unchanged if water is added immediately. The solution in concentrated hydrochloric acid gives no crystals at once, but after standing an hour at 0° white crystals are deposited in considerable quantity. These have all the properties of carbonylaminophenol; they are not soluble in water nor are they decomposed by water, but dissolve readily in alkalies with acids. The alkaline solution gives white crystals, containing no chlorine, which are undoubtedly carbonylaminophenol. Even by the use of a solution of hydrochloric acid saturated at 0° , it was not possible to obtain the hydrochloride in the solid form. It is therefore probable that Seidel mistook the crystals of carbonylaminophenol, for those of the hydrochloride of chlormethenylaminophenol. That the salt exists in solution, being very soluble, was shown by the action of nitric acid on a freshly prepared

solution of the hydrochloride, and by the formation of a chlorplatinate.

A few drops of chlormethenylaminophenol were dissolved in about two volumes of concentrated hydrochloric acid. No crystals were formed, even on cooling the solution with ice and salt; the addition of nitric acid (sp. gr. 1.28) caused an immediate heavy white precipitate, which was undoubtedly the nitrate, since on the addition of water the crystals decomposed, leaving an oil—chlormethenylaminophenol. The formation of the nitrate in this way must be considered a true ionic reaction, and shows clearly that the bodies under discussion are true salts.

Chlormethenylaminophenol Chlorplatinate,



0.5 gram of chlormethenylaminophenol was dissolved in about 4 cc. of ice-cold concentrated hydrochloric acid and added to a solution of 0.5 gram of platinic chloride dissolved in 3 cc. of concentrated hydrochloric acid. After ten minutes the ice-cold solution had deposited a considerable quantity of orange-colored crystals. These were drained on a platinum cone, pressed out quickly on a clay plate, and dried over sulphuric acid. The crystals are stable in the absence of water, but the latter quickly decomposes the body into its constituents.

0.0529 gram gave 0.0141 gram Pt.

0.2334 gram gave 0.0619 gram Pt.

	Calculated for (C ₇ H ₅ ClNO) ₂ PtCl ₆ .	I.	Found.	II.
Pt	26.79	26.69		26.52

PART II.

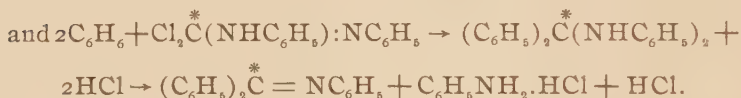
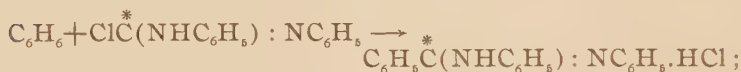
*The Hydrochlorides of Carbodiphenylimide.*¹

Carbodiphenylimide unites with hydrochloric acid, as Lengfeld and Stieglitz have found,² in two proportions; namely, to form the monohydrochloride, C(C₆H₅N)₂.HCl, and the dihydrochloride, C(C₆H₅N)₂.2HCl. From the fact that the monohydrochloride gives with sodium ethylate, smoothly

¹ Preliminary reports: Ber. d. chem. Ges., 30, 1090, 1682.

² This JOURNAL, 17, 107.

and quantitatively, ethyl isocarbaniide, $C_2H_5OC(NHC_6H_5) : NC_6H_5$, Lengfeld and Stieglitz¹ have thought it quite probable that, in the monochloride, the chlorine is bound to carbon and not to nitrogen; that it has consequently the constitution, $Cl.C(NHC_6H_5) : NC_6H_5$. Similarly, in the dihydrochloride, one, at least, and perhaps both chlorine atoms are bound to carbon thus: $ClC(NHC_6H_5) : NC_6H_5.HCl$ or $Cl_2C(NHC_6H_5)_2$. In the hope of obtaining further evidence on this point, I have studied the action of the above hydrochlorides on benzene, in the presence of aluminium chloride. According to the view just expressed, it seemed possible, in this way, to obtain benzamidine (or benzophenone) derivatives,² according to:



¹ *Loc. cit.*; and Stieglitz: Ber. d. chem. Ges., **28**, 537.

² Since Friedel and Crafts' syntheses with aluminium chloride involve almost universally, the use of an alkyl or acyl haloid—that is, substances containing the group CCl , or its equivalent, it is thought that the reaction can be used to prove the presence of such a CCl group, in a chloride of doubtful constitution. This method of proof had, in fact, been previously used, most notably by Gattermann (Ann. Chem. (Liebig), **244**, 47), in the closely allied case of the hydrochlorides of the isocyanates. According to their action on benzene derivatives, in the presence of aluminium chloride, they have been generally assumed to be chlorformanilides (*Vide*, Meyer and Jacobson: Lehrbuch, Vol. II., p. 199; Richter-Anschütz, 8th ed., Vol. II., p. 76)



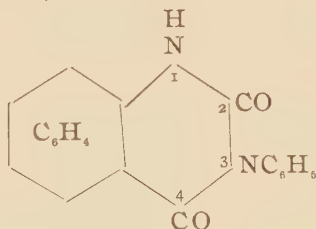
In fact, in their action on benzene, in the presence of aluminium chloride, they resemble substances which undoubtedly have a similar constitution, such as chlorformmethylanilide, $RNCH_3.COCl$. In the few cases where Friedel and Crafts' synthesis has succeeded without the use of an alkyl or acyl haloid—for instance, with phenyl isocyanate (Leuckart: Ber. d. chem. Ges., **18**, 873) and with ethylene (Balson: Bull. Soc. chim., **31**, 541), it appeared most probable that such haloids were first formed by the addition of hydrogen chloride, which is always present (Leuckart: *Loc. cit.*; Gattermann: *Loc. cit.*).

The two most important interpretations of Friedel and Crafts' reaction agree with this conclusion: the older one (Friedel and Crafts: Ann. Chim. [6], **14**, 457; Meyer u. Jacobson: Lehrbuch, II, 98) requiring a chlor-carbon group (CCl) to react with the supposed intermediate organic derivative of aluminium chloride, *e. g.*, $C_6H_5.Al_2Cl_5$; the new and interesting view of Nef (Ann. Chem. (Liebig), **298**, 222) ascribing the condensation to the addition of phenyl and hydrogen (C_6H_5 and H) to the nascent double bonds of unsaturated derivatives, and thus postulating the presence of the same chlor-carbon group, to make a "nascent double bond" at all possible.

However no benzamidine nor benzophenone derivatives are formed. The chief product of the reaction is a yellow base, of the composition $C_{26}H_{20}N_4$, the constitution of which has been established by a thorough study of its reactions, its decomposition-products, and finally by its direct synthesis. The results leave no doubt that a Friedel and Crafts' condensation actually takes place involving the carbon atom marked with a star (*) ; only instead of attacking the benzene itself, it enters one of the benzene nuclei of a second molecule of carbodiphenylimide. The composition of the new body is the same as that of carbodiphenylimide itself, but preliminary determination showed the body to have double the molecular weight of carbodiphenylimide. It has therefore the composition $C_{26}H_{20}N_4$. Several polymers of carbodiphenylimide are described in the literature ;¹ but the body obtained by the action of aluminium chloride differs markedly from all of these and from carbodiphenylimide itself. The body $C_{26}H_{20}N_4$ is a base, forming yellow crystals, which dissolve readily in dilute hydrochloric acid, to form a yellow solution, that soon becomes colorless. Alkalies precipitate from the colorless solution a white base, having the composition $C_{20}H_{16}N_3O$, while the aqueous solution contains aniline. Saponification of an aniline group has therefore taken place :



By further saponification of the substance $C_{20}H_{16}N_3O$ by prolonged heating, in a sealed tube, with concentrated hydrochloric acid, a good yield of a body $C_{14}H_{10}N_2O_2$, which proved to be identical with the 3-phenyl-2-4-diketotetrahydroquinazoline of Busch² and Paal,³



¹ Weith: Ber. d. chem. Ges., **7**, 10; Schall: *Ibid.*, **25**, 2886; Cf. Von Miller u. Plöchl: *Ibid.*, **28**, 1004.

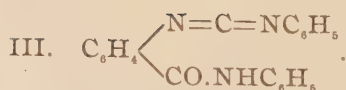
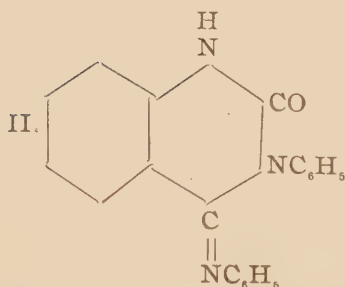
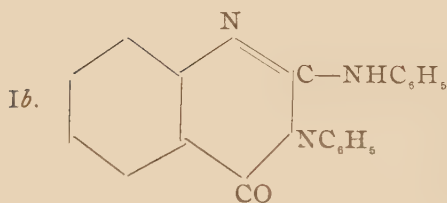
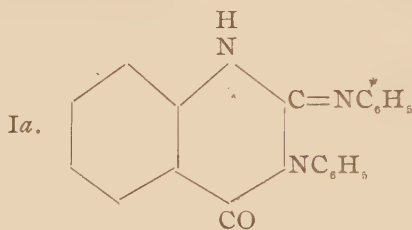
² J. prakt. Chem., **51**, 265.

³ Ber. d. chem. Ges., **27**, 978.

was obtained, and at the same time aniline was formed. The action of concentrated hydrochloric acid on the white base, $C_{20}H_{15}N_3O$, is therefore expressed by the equation :



The compound $C_{20}H_{15}N_3O$ must consequently have the constitution expressed by one of the following structural formulas:



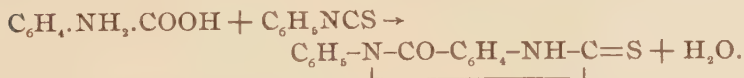
Formula III is excluded by the following properties of the body : (1) it is a strong base soluble in dilute acids ; (2) it remains unchanged when boiled with concentrated hydrochloric

ric acid, as also when boiled with aniline. *Ia* and *Ib* differ from II only in the position of the aniline group attached to the quinazoline ring. Since the aniline group in position 2 (*Ia* or *b*) forms a derivative of triphenylguanidine, which is very stable toward saponifying agents, while in position 4 (II), we have a derivative of *s*-benzenyldiphenylamidine, which is readily saponified to benzanilide,¹ formula I (*a* or *b*) was supposed to be the more probable one, and this view was tested by preparing a body of the composition and constitution I. It proved to be identical with the white base, $C_{20}H_{16}N_3O$. The compound is, therefore, either 2-phenylimido-3-phenyl-4-ketotetrahydroquinazoline, *Ia*; or 2-phenyl-amido-3-phenyl-4-ketodihydroquinazoline, *Ib*.

Two substances corresponding to *Ia* and *Ib* are so closely related and pass over so readily into one and the same form that only one form is usually, if not always, known. Experiments will be described below, the object of which is to distinguish between these two forms.

With methyl iodide, the body gives the 1(N) methyl derivative, indicating, perhaps, formula *Ia*, on which account, to avoid the duplication of cumbersome names, that of formula *Ia* will be used in referring to the body and its derivatives. As, however, addition of the methyl iodide to the double bond between carbon and nitrogen, and subsequent splitting off of hydrogen iodide, may take place instead of direct substitution, this reaction is not free from objection, as a means of determining constitution, so that formula *Ib* is not absolutely excluded.

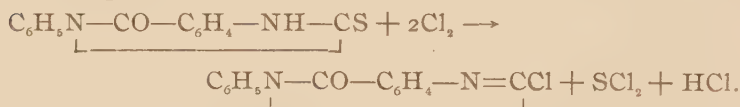
The synthetic proof of the constitution of the white base, $C_{20}H_{16}N_3O$, was furnished in the following manner: From anthranilic acid and phenyl mustard-oil, *o*-phenylthioureido-benzoic acid was prepared. The latter, by loss of water, readily gives 2-thio-3(N)-phenyl-4-ketotetrahydroquinazoline:



This compound, as also its thio-ether, 2-ethylthio-3(N)-phenyl-4-ketodihydroquinazoline, proved to be unusually in-

¹ Wallach: Ann. Chem. (Liebig), 184, 85.

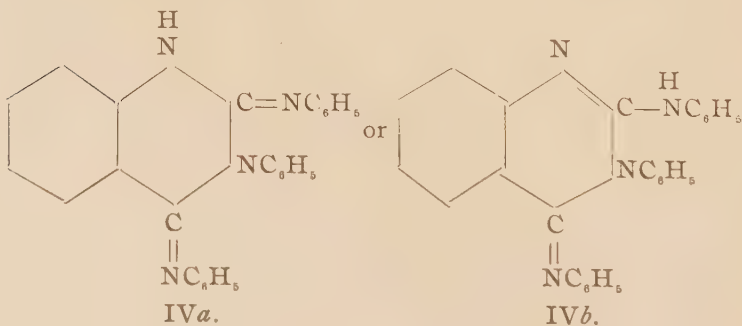
active towards aniline; both, however, when heated with aniline in a sealed tube to 300° , gave a small amount (5 to 10 per cent. yield) of the compound $C_{20}H_{16}N_3O$, with evolution of hydrogen sulphide or ethylmercaptan. Since the thio-bodies reacted with aniline with such great difficulty, another method of synthesis was tried, and this gave, without difficulty, the desired compound. If one treats the 2-thio-3(N)-phenyl-4-ketotetrahydroquinazoline with dry chlorine, in the presence of chloroform, the sulphur is easily replaced by chlorine, with the formation of 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline, thus:



The chloride so obtained gave, smoothly and quantitatively, by heating with aniline, the compound $C_{20}H_{16}N_3O$. This body has, therefore, the aniline group in position 2, [formula I (*a* or *b*)].

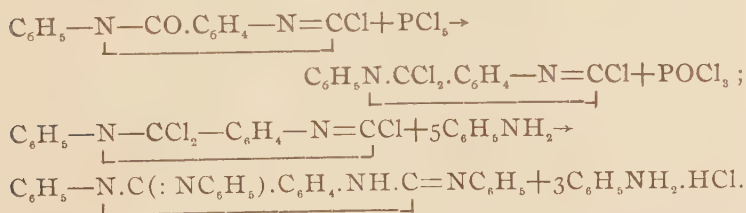
This synthesis shows at the same time that the quinazoline double ring is not formed in the heating of this compound with concentrated hydrochloric acid in the sealed tube; but that it exists previously in the bases obtained from carbodiphenylimide.

The yellow base, $C_{26}H_{20}N_4$, obtained by the action of aluminium chloride on carbodiphenylimide, gives, by saponification with cold dilute hydrochloric acid, aniline and the quinazoline derivative, $C_{20}H_{16}N_3O$, just discussed, and must therefore be represented by one of the closely allied formulas



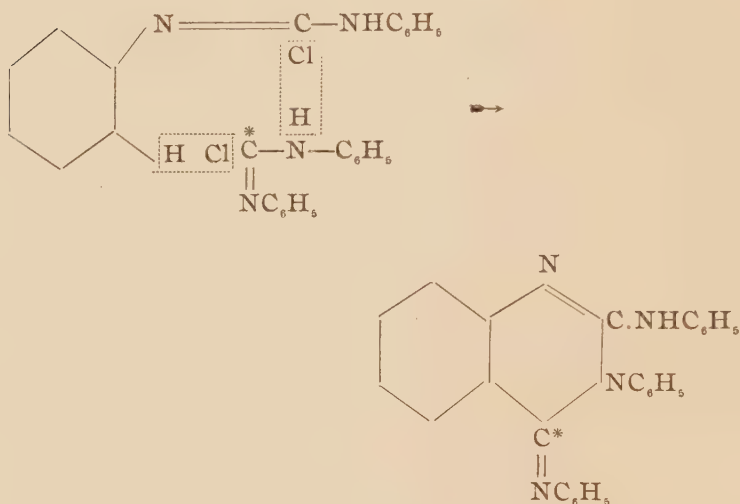
It is therefore 2-4-diphenylimido-3(N)-phenyltetrahydroquinazoline (IV *a*) or 2-phenylamido-3(N)-phenyl-4-phenylimidodihydroquinazoline (IV *b*). The yellow compound, $C_{26}H_{20}N_4$, for which the above closely related formulas have been determined, exists in two forms—prisms (α -form) melting at 171° , and rhombic plates (β -form) melting at 184° . With a single possible exception, described below, the two forms have the same chemical properties, but their solubilities, in various organic solvents, are quite different; and when either form is dissolved in any solvent it is always the form which is less soluble in that solvent that crystallizes out. When heated above its melting-point the α -form is converted into the β -form. Whether the two forms are constitutionally different according to IV *a* and *b*, or stereoisomeric phenylimido derivatives, or finally only dimorphic modifications of a single substance, has not yet been definitely determined. This will be discussed in connection with the experiments on this point.

The constitution developed for the yellow base, $C_{26}H_{20}N_4$, was confirmed synthetically in the following way: The above-mentioned 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline was treated with phosphorus pentachloride in order to replace the oxygen atom by chlorine. By treating the compound so obtained with aniline, a small amount of the yellow base, $C_{26}H_{20}N_4$, was obtained as prisms (α -form), melting at 171° , which after melting and cooling crystallized in the β -form, melting at 184° . The body had all the properties of the compound obtained from carbodiphenylimide. The reactions take place thus:



The formation of 2-4-phenylimido-3(N)-phenyltetrahydroquinazoline by the action of aluminium chloride on the hydro-

chloride of carbodiphenylimide may be represented in the following simple manner :



On the basis of the prevalent views of the Friedel and Crafts' synthesis,¹ the entrance of the carbon atom C* into the benzene ring, by the action of aluminium chloride, is in the best agreement with the views of Stieglitz and Lengfeld that in the monohydrochloride of carbodiphenylimide the chlorine is bound to carbon ; that it is therefore to be regarded as chloroformyldiphenylamidine, $\text{ClC}(\text{NHC}_6\text{H}_5):\text{NC}_6\text{H}_5$.

By using carbodiphenylimide, instead of its hydrochloride, the yield of the yellow base is very materially reduced, being only one-tenth as large as that obtained from the monochloride (5 per cent. instead of 50 per cent. of the theoretical yield) and here, as in Leuckart's results with phenyl isocyanate,² benzene and aluminium chloride, the formation of any of the quinazoline compounds at all may be ascribed to the liberation of some hydrogen chloride, which would convert the carbodiphenylimide into the monochloride.

That the chlorine atom in question becomes attached to car-

¹ *Vide* note p. 22.

² *Loc. cit.*

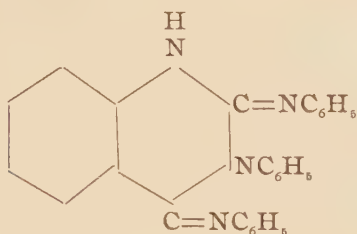
bon *before* the possible saturation of the free nitrogen valencies, by an excess of hydrogen chloride, as perhaps according to the equation,

$C(:NC_6H_5.HCl)_2 + HCl \rightarrow Cl.C(:NC_6H_5.HCl)(NHC_6H_5.HCl)$,
is proved by the fact that an excess of hydrogen chloride must be avoided in order to accomplish the formation of the quinazoline compound.

EXPERIMENTAL PART.

The Action of Aluminium Chloride on the Chlorides of Carbodiphenylimide.

2-4-Diphenylimido-3(N)-phenyltetrahydroquinazoline,



Carefully dried hydrogen chloride was passed into a solution of freshly prepared carbodiphenylimide (10 grams) in benzene (70 cc.) free from thiophene until a heavy precipitate was obtained. As Lengfeld and Stieglitz¹ have shown, this precipitate consists of a mixture of the two chlorides of carbodiphenylimide, while the benzene solution still contains unchanged imide in solution. The mixture so obtained was diluted with 100 cc. of pure carbon bisulphide; heated to boiling; and 10 grams of aluminium chloride added, in portions of 2 grams in the course of three-quarters of an hour. After heating for a quarter of an hour longer, the nearly colorless benzene and carbon bisulphide solution, which still contained a little unchanged carbodiphenylimide, was poured from the dark-brown mass that had separated during the reaction. The latter was treated with dilute sodic hydrate and with water to remove aluminium compounds; and the yellow resi-

¹ This JOURNAL, 17, 107.

due, excepting a small insoluble portion, was dissolved in carbon bisulphide, in which the product is now very easily soluble. On evaporating the solution at the ordinary temperature, yellow crystals of 2-4-diphenylimido-3(N)-phenyltetrahydroquinazoline separated, the amount of which was increased by adding alcohol.

The body was purified by dissolving in benzene and adding ligroin (b. p. 40-60°). With a small amount of ligroin, a small quantity of sulphur-yellow, rhombic plates (β -form), melting at 184°, was obtained, while the filtrate with more ligroin gave a far greater amount of yellow prisms (α -form), melting at 171°.

0.2097 gram of the α -form gave 0.6150 gram CO_2 , and 0.0966 gram H_2O .

0.1062 gram of the α -form gave 0.3141 gram CO_2 , and 0.0544 gram H_2O .

0.1976 gram of the α -form gave 24.7 cc. of N_2 at 17.5° and 752.4 mm.

	Calculated for $\text{C}_{18}\text{H}_{10}\text{N}_2$ or $\text{C}_{28}\text{H}_{20}\text{N}_4$.	I.	Found. II.	III.
C	80.41	80.00	80.66	
H	5.15	5.20	5.68	
N	14.44			14.38

As has been mentioned, the yield of the above body depends, to a great extent, upon the amount of hydrogen chloride present during the reaction with aluminium chloride. Under favorable conditions the yield is about 50 per cent. An excess of hydrogen chloride must be avoided. In cases in which very much more than one equivalent of hydrogen chloride was passed into the benzene solution of carbodiphenylimide very little, or with a great excess even none, of the quinazoline resulted. The best yield was obtained by dissolving equivalent quantities of carbodiphenylimide and its pure dry dihydrochloride¹ in benzene, thus securing exactly one equivalent of hydrogen chloride. This procedure is unnecessary if, in the preparation of the chloride, the current of hydrogen chloride is stopped before any of the heavy precipitate first formed begins to dissolve, as at this point

¹ Lengfeld and Stieglitz: This JOURNAL, 17, 107.

approximately one molecule of the gas has been absorbed. It has been found that the best method of separating the body from the by-products, which are chiefly unchanged carbodiphenylimide, polymeric carbodiphenylimide and carbanilide, the latter being formed by the action of water on carbodiphenylimide, consists in treating the mixture, left after removing aluminium compounds, as above described, with cold alcohol in small portions, and dissolving the residue, which is chiefly the new body, in hot acetone and adding 80 per cent. alcohol. On standing, most of the substance separates in prisms of the α -form.

The action of aluminium chloride either on free carbodiphenylimide or on its pure dichloride, in the presence of benzene and carbon bisulphide, gives very much smaller yields of the body, $C_{26}H_{20}N_4$, than when the reaction is carried out in the presence of approximately *one* equivalent of hydrogen chloride.

Two grams of pure freshly made and freshly distilled carbodiphenylimide were dissolved in benzene and carbon bisulphide, and the solution treated with aluminium chloride in the usual manner. From the reaction-product 0.107 gram ($=5\frac{1}{2}$ per cent.) of the body, $C_{26}H_{20}N_4$, was obtained.

Five grams of the pure dihydrochloride of carbodiphenylimide treated, in the presence of benzene and carbon bisulphide, with aluminium chloride in the usual way, gave 0.47 gram ($=12\frac{1}{2}$ per cent.) of the yellow body $C_{26}H_{20}N_4$. The theoretical significance of these results has already been discussed.

The molecular weight determination of the α -form of the yellow body, $C_{26}H_{20}N_4$, by the lowering of the freezing-point of benzene, showed the body to have the double formula :

	Benzene. Grams.	Substance. Gram.	Lowering.	Mol. weight. Found.
I.	35.62	0.3356	0.136°	347
	35.62	0.6086	0.240°	356
II.	35.44	0.5494	0.223°	348
	35.44	0.8184	0.335°	354

Calculated for $C_{13}H_{10}N_2$, 194 ; for $C_{26}H_{20}N_4$, 388.

The determination by the elevation of the boiling-point of chloroform,¹ led to the same conclusion :

Chloroform. Grams.	Substance. Gram.	Elevation.	Mol. weight. Found.
28.7	0.6242	0.223°	360
28.7	0.9904	0.344	372

Analysis of the β -form showed that it has the same composition as the α -form :

0.1830 gram of the β -form gave 24.2 cc. N_2 at 26° and 745.5 mm.

	Calculated for $C_{13}H_{10}N_2$ or $C_{26}H_{20}N_4$.	Found.
N	14.44	14.48

The molecular weight determination of the β -form, by the freezing-point method in benzene, also showed the double formula to be the correct one :

Benzene. Grams.	Substance. Gram.	Lowering.	Mol. weight found.
20.3	0.4046	0.271°	368
20.3	0.6701	0.466°	354

The two forms (α and β) are converted into each other with the greatest ease. When the α -form is heated to its melting-point and allowed to cool slowly, it crystallizes in rhombic plates of the β -form, and these when heated again melt sharply at 184°. The α -form dissolves in benzene very readily, but the clear solution soon deposits rhombic plates of the β -form, melting at 184°. Either form, crystallized from any of the following solvents: alcohol, acetone, ligroin, ethyl acetate, acetoacetic ester, acetic anhydride or aniline, gives *only* the α -form. The fact that crystallization from benzene gave one form, while from alcohol the other was obtained, caused a determination of the solubility of each form, in each of these solvents, to be made. At the temperature of the room, a saturated solution in benzene contains :

α -Form (prisms). Per cent.	β -Form (plates). Per cent.
14.2	7.3

A saturated solution in alcohol contains :

¹ Molecular elevation taken as 36.6°; Beckmann : Ztschr. phys. Chem., 8, 227.

α -Form.
Per cent.
0.17

β -Form.
Per cent.
0.24

The result shows that, in both cases, it is the less soluble form, which crystallizes from the solvent. Finding later that the α -form is obtained by crystallizing from acetone, it was predicted that this form would be less soluble in this solvent. Experiments confirmed this.

A saturated solution in acetone contains :

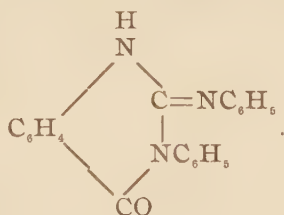
α -Form.
Per cent.
I. 5.73
II. 5.89

β -Form.
Per cent.
III. 6.74
IV. 7.33

The β -form dissolves in acetone quite readily, but the α -form separates so quickly, that in determination III, this began to take place during the filtration; hence the low result.

The body $C_{26}H_{20}N_4$ is remarkably stable towards heat, distilling unchanged in a vacuum above 340° . The distillate solidifies to an amber-like amorphous mass, which has no definite melting-point, beginning to soften at about 100° . On standing and especially on warming and also by the use of solvents, the amorphous substance is readily converted, according to the conditions, into the α - or β -crystalline form. The results of these experiments led to the conclusion that the two forms are physical or crystallographic modifications of the same substance. On the other hand a most surprising difference was found in the behavior of benzene solutions of the two forms towards phenyl isocyanate, as will be discussed later, a fact which would seem to point to a chemical difference between the two forms.

2-Phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline,



Both forms of the yellow body, $C_{26}H_{20}N_4$, dissolve in dilute hydrochloric acid, forming a bright yellow solution which becomes perfectly colorless on standing in the cold several hours, or in a few minutes at the boiling-point. Alkalies now precipitate from the colorless solution a white base, which has been shown to be 2-phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline, $C_{20}H_{15}N_3O$, while aniline remains in the aqueous solution. The aniline was identified, after distilling it off with steam, by the bleaching-powder reaction, by the isonitrile test, and by conversion into benzanilide. The latter melted at 160° , and the melting-point remained unchanged on mixing with pure benzanilide, made in the usual way. The new body is a decided base, dissolving easily in dilute acids, from which alkalies precipitate it unchanged. Recrystallized from alcohol, it is obtained in colorless needles, melting at 163° . It is easily soluble in benzene, chloroform, and carbon bisulphide; less soluble in alcohol and ether, and almost insoluble in low-boiling ligroin and water.

0.1225 gram gave 0.3460 gram CO_2 , and 0.0545 gram H_2O .

0.1042 gram gave 12.65 cc. N_2 at 23° and 759.7 mm.

	Calculated for $C_{20}H_{15}N_3O$.	Found.
C	76.62	77.05
H	4.82	4.98
N	13.45	13.75

The reaction has taken place according to the following equation:



A quantitative experiment gave an almost theoretical yield of the body $C_{20}H_{15}N_3O$,—77.9 instead of 80.6 per cent.

The body, $C_{20}H_{15}N_3O$, is saponified but very slowly by boiling with concentrated hydrochloric acid or with alcoholic potash. For the further saponification, 5.3 grams of the substance, with 12 cc. of concentrated hydrochloric acid, was heated in a sealed tube seven hours at 160° – 180° . On cooling, large colorless plates (3.1 grams) had formed. These were separated from the brown acid solution, which latter gave with alkali 0.4 gram of the unchanged base. The alka-

line filtrate on extraction with ether gave aniline, which was identified by its boiling-point, 183° , and by the melting-point 160° , of the benzanilide formed by treating it with benzoyl chloride. The melting-point was not changed by mixing with synthetic benzanilide.

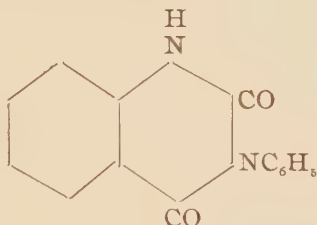
The above-mentioned colorless crystals, after recrystallization from boiling alcohol, formed needles melting at 272° .

0.1849 gram gave 0.4775 gram CO_2 , and 0.0718 gram H_2O .

0.1303 gram gave 13.8 cc. N_2 at 16° and 742.1 mm.

	Calculated for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$.	Found.
C	70.54	70.44
H	4.23	4.34
N	11.79	12.09

The composition and melting-point are those of 2-4-diketo-3(N)-phenyltetrahydroquinazoline,¹



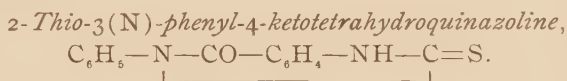
The analyzed body, like that described by Busch and by Paal, shows in alkaline solution an extraordinary blue fluorescence. The phenomenon is especially beautiful in dilute solution; in stronger solutions in the presence of much alkali it is much fainter. As a complete proof of the identity of the body obtained by me, with that of Busch and Paal, the body was made according to the directions of the latter from anthranilic acid and phenyl isocyanate. By mixing the quinazoline bodies obtained in both ways the melting-point (273°) remained unchanged; all other properties were also identical. Hence it follows that the saponification has taken place thus:



The method of synthesis and its properties leave no doubt

¹ Busch: J. prakt. Chem. [2], 51, 265; Paal: Ber. d. chem. Ges., 27, 978.

concerning the constitution of 2-4-diketotetrahydroquinazoline—the body $C_{14}H_{10}N_2O_2$. The constitution of the body, $C_{20}H_{16}N_2O$, must therefore be represented by one of the formulas Ia, Ib, II or III, page 24. As has already been mentioned, formula III is excluded by the properties of the body, while, between I(a or b) and II, the former was given the preference and the constitution proved by preparing such a compound synthetically. It was found to be identical with the base $C_{20}H_{16}H_3O$. The first step in the synthesis was the preparation of



Anthranilic acid (10 grams) was dissolved in 100 cc. of alcohol and 50 cc. of water, containing a little over one molecule of potassic hydrate, and phenyl mustard-oil (9 grams = 1 mol.) added. Most of the mustard-oil goes into solution at once. After standing two or three hours, with occasional shaking, the reaction is complete. Without alcohol the action is extremely slow, but with an excess of alcohol much phenylthiourethane is formed. Water is added after the reaction is complete. The solution is filtered from a small oily precipitate, when necessary, and saturated with carbon dioxide. The nearly white heavy granular precipitate, which forms very slowly, is complete only after several hours. For further purification the product was dissolved in dilute alkali and again treated with carbon dioxide, which now causes a rapid separation of a voluminous precipitate.

By its analysis and behavior, the body was shown to be the above-mentioned thioquinazoline.¹ It is a very weak acid, like all similar thioamides; it dissolves in alkalies (without fluorescence), and is then precipitated immediately by carbon dioxide; it is difficultly soluble in most organic solvents, and crystallizes from a mixture of alcohol and acetone in almost colorless rectangular plates, which melt without decomposition above 300°.

0.1540 gram gave 15.7 cc. N_2 at 23° and 748.7 mm.

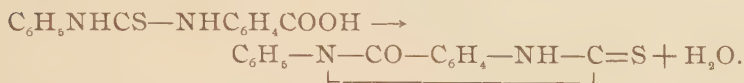
¹ Vide Stewart: J. prakt. Chem. [2], 49, 415.

	Calculated for $C_{14}H_{10}N_2SO$.	Found.
N	11.05	11.38

In the action of phenyl mustard-oil on anthranilic acid, the first product is evidently *o*-phenylthioureïdobenzoic acid :



The latter is stable in alkaline solution, but in the small quantity in which it is liberated in the solution by the weaker carbonic acid, it loses water, forming the quinazoline derivative :



The formation of 2-4-diketo-3(N)-phenyltetrahydroquinazoline, by evaporating a solution of the ammonium salt of phenylureïdobenzoic acid,¹ must depend in a similar manner upon the gradual liberation of the acid by the slow decomposition of the salt in solution. The intermediate thioureïdobenzoic acid may be isolated by treating the reaction-product of anthranilic acid and mustard-oil, with hydrochloric acid instead of carbonic acid. This causes an immediate precipitate, which contains some quinazoline. To remove the latter the precipitate is dissolved in aqueous sodium bicarbonate, in which the quinazoline is insoluble, quickly filtered, and again precipitated with hydrochloric acid. The thioureïdo acid so prepared, after being dried on a clay plate, was crystallized by dissolving in acetone and adding ligroïn (40°–60°). The colorless needles are undoubtedly *o*-phenylthioureïdobenzoic acid. The acid melts with decomposition at 185°–190°, when plunged into the hot bath. It is readily soluble in sodium bicarbonate, and on treating the solution with carbon dioxide the thioquinazoline slowly separates out as before.

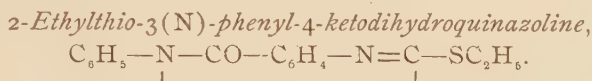
By oxidation with potassium permanganate Busch² converted 2-thiotetrahydroquinazoline into 2-4-diketotetrahydroquinazoline. Similarly, 2-thio-3(N)-phenyl-4-ketotetrahy-

¹ Paal : *Loc. cit.*

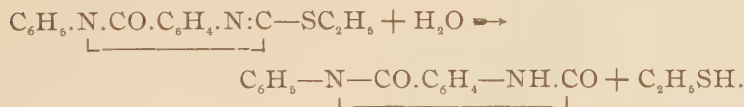
² J. prakt. Chem. [2], 51, 128.

Since in the thio-body the sulphur atom is in position 2, it follows that the aniline group is also in 2 and not in 4; that, therefore, formula I(a or b), page 24, must represent the body $C_{20}H_{16}N_2O$.

As the thio-ethers¹ of thioanilides are especially reactive toward aniline, the ethyl ether of the above thio-body was made and treated with aniline, in the hope of obtaining a better yield of the body, $C_{20}H_{16}N_2O$, synthetically.



2-Thio-3(N)-phenyl-4-ketotetrahydroquinazoline was covered with alcohol, brought into solution by 30 per cent. potassic hydrate, and somewhat more than the calculated amount of ethyl iodide added. The solution after boiling half an hour and filtering from a slight residue gave, on cooling, long colorless needles of the thio-ether, the amount of which was increased to an almost theoretical yield by evaporating the mother-liquor. After a crystallization from somewhat dilute alcohol the substance is pure. It forms long, colorless needles melting at 114° . By boiling with dilute hydrochloric acid, ethylmercaptan (recognized by its odor) was given off, and the residue gave, with dilute alkali, a solution having the characteristic violet fluorescence of 2-4-diketo-3(N)-phenyltetrahydroquinazoline:



The method of preparation and the behavior with hydrochloric acid show that the body has the constitution given.

0.1592 gram gave 14.25 cc. N_2 at 24° and 748 mm.

	Calculated for $C_{18}H_{14}N_2SO$.	Found.
N	9.95	9.93

As a further means of confirming the constitution of my

¹ Wallach; Ber. d. chem. Ges., 12, 1061.

thio-ether,¹ I have also made the corresponding methyl ether, $\text{C}_6\text{H}_5\text{—N—CO.C}_6\text{H}_4\text{.N : C—SCH}_3$, in exactly the same way

as that by which the ethyl ether was obtained. It forms long needles melting at 125° , easily soluble in alcohol.

0.1032 gram gave 0.0888 gram BaSO_4 .

S	Calculated for	Found.
	$\text{C}_{15}\text{H}_{12}\text{N}_2\text{SO}$.	
	11.94	11.83

Boiled with dilute hydrochloric acid it is slowly saponified, giving methylmercaptan and leaving the diketoquinazoline. The isomeric 1(N)-methyl body, 1(N)-methyl-2-thio-3(N)-phenyl-4 ketotetrahydroquinazoline,



has recently been made by Fortmann,² from methylanthranilic acid, and melts at $288^\circ\text{--}289^\circ$. There can therefore be no doubt as to the nature of the thio-ether obtained by me.

The Action of Aniline on 2-Ethylthio-3(N)-phenyl-4-ketodihydroquinazoline.

To accomplish a reaction with aniline 2-ethylthio-3(N)-phenyl-4-ketodihydroquinazoline must be heated in a sealed tube. 1 gram of the ether was heated to 300° for eight hours with 5 grams of aniline. On opening the tube the odor of mercaptan was very strong. After distilling off the excess of aniline, the larger part of the dark-red residue dissolved in hot dilute hydrochloric acid, forming a dark-green solution. By fractional precipitation with alkali a small amount of a dark-red mass was obtained which contains a dye that dissolves in alcohol forming a red solution, having a remarkable orange-colored fluorescence. Acids change the color to green. The dye has not yet been studied further. From the principal part of the precipitate with alkali, after decolorizing by boiling the alcoholic solution with animal charcoal, nearly colorless needles melting at 162° .5 were obtained; these mixed with pure 2-phenylimido-3(N)-phenyl-4-ketotetrahydroquin-

¹ Vide Ber. d. chem. Ges., **30**, 1690.

² J. prakt. Chem., **55**, 132.

soluble in chloroform and benzene, less in alcohol and ether, and difficultly soluble in ligroin (40°–60°). From a solution in benzene the body is precipitated by ligroin in needles. It may be recrystallized from boiling alcohol unchanged,—a fact which shows how firmly the chlorine atom is held in the molecule.

An attempt to determine the chlorine according to Carius was unsuccessful. After heating for six hours at 240° and for four hours at 340° a considerable amount of an orange-colored compound, insoluble in acids, remained unoxidized. A chlorine determination was easily accomplished in a very short time by boiling, for thirty minutes, a solution of the weighed substance with 20 cc. of pure methyl alcohol in which 0.5 gram of sodium had been dissolved. The solution, from which common salt had separated, was diluted with water, acidified with nitric acid, and titrated with silver nitrate, according to Volhard.

0.1863 gram required 7.35 cc. $\frac{N}{10}$ AgNO₃.

0.4260 gram required 16.53 cc. $\frac{N}{10}$ AgNO₃.

	Calculated for C ₁₄ H ₉ N ₃ ClO.	I.	Found.	II.
Cl	13.84	13.79		14.00

2-Dichlor-3(N)-phenyl-4-ketotetrahydroquinazoline,

$$\text{C}_6\text{H}_5\cdot\text{N}\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{C}\cdot\text{Cl}_2$$
└──────────┘

Like chlormethenylaminophenol, the above analyzed monochlorquinazoline gives, with dry hydrogen chloride, a dichloride, which in all probability is to be represented by the above formula. Carefully dried hydrogen chloride was passed into a solution of 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline in benzene. A white precipitate resulted which, after filtering and washing with ligroin as quickly as possible, was pressed on a clay plate for a minute or so and then dried in a vacuum over sulphuric acid. On opening the desiccator, a very little hydrochloric acid was noticed, showing slight decomposition. The substance melts at 140° with decomposition. In contact with water, it readily loses one molecule of acid, giving the original quinazoline chloride.

For the analysis the weighed substance was covered with water and titrated with alkali, methyl orange being used as an indicator.

0.2901 gram required 9.6 cc. $\frac{N}{10}$ alkali.

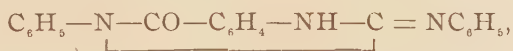
0.2800 gram required 9.0 cc. $\frac{N}{10}$ alkali.

	Calculated for $C_{14}H_9N_2ClO.HCl$.	I.	Found.	II.
Cl	12.09	11.73		11.40

In the preparation of 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline from the thio-derivative, the yellowish body insoluble in chloroform remaining after the treatment with chlorine is undoubtedly the above dichloride.

Synthesis of 2-Phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline.

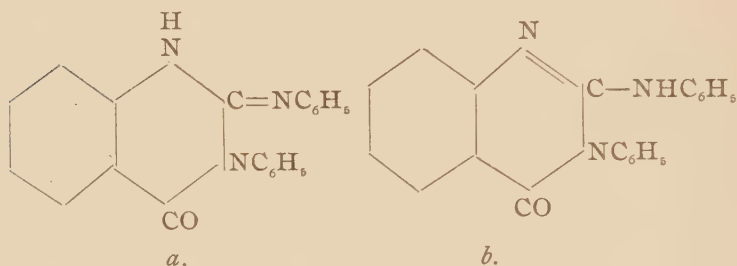
2-Chlor-3(N)-phenyl-4-ketodihydroquinazoline dissolves readily in aniline, but the reaction with it goes on very slowly in the cold; only after two days had the mixture solidified. At the boiling-point of aniline the reaction is complete in fifteen minutes; on cooling the product solidifies to a crystalline mass, which dissolves readily in aqueous hydrochloric acid, with the exception of a small dark-colored residue. The nearly colorless filtrate gives with alkalies an almost white precipitate which, after recrystallization from alcohol, forms colorless needles melting at 163° . The body thus obtained was identical in every respect with 2-phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline,



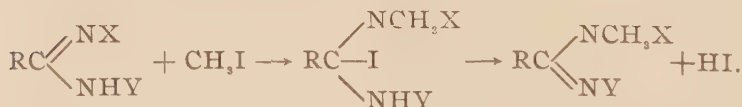
obtained by the saponification of the yellow base, $C_{26}H_{20}N_4$, which is formed by the Friedel and Crafts reaction from the hydrochloride of carbodiphenylimide. When the substances made in both ways are mixed there is no change in the melting-point. Thus the absolute identity of the substances is established. The new method of preparing 2-phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline is much to be preferred to the old, as the yields in all of the transformations are

excellent. A large part of the substance used was prepared in this way.

This synthesis confirms the constitution already established by the other two syntheses from the thio-derivatives. The body, $C_{20}H_{16}N_3O$, has, therefore, one of the so-called tautomeric forms *a* or *b*:



The question still remained: Which of these two formulas is to be ascribed to the body in hand? The question is very much like that concerning the constitution of the amidines, the diazoamido bodies, etc. Of all these analogous bodies, experiment has shown that, with a very few doubtful exceptions, but one of the two possible forms exists. In his work on amidines, von Pechmann¹ has used the reaction with methyl iodide to determine the position of the "labile" hydrogen atom, assuming that the methyl group takes the place occupied by the hydrogen atom. This method is, however, not entirely free from objection, since it is possible that the methyl iodide may first be added to the double bond, just as hydrogen haloid is added to the double bond of the similarly constituted imido-esters; the loss of hydriodic acid would then give a body having the methyl attached to the nitrogen atom which originally held no hydrogen; thus,



Direct substitution of methyl for hydrogen would give

¹ Ber. d. chem. Ges., 28, 869, 2362.

$$\text{RC} \begin{array}{l} \diagup \text{NX} \\ \diagdown \text{NCH}_3\text{Y} \end{array}$$
 The same amidine could thus give two isomeric methyl derivatives; in fact where X and Y are very similar, two alkyl derivatives are obtained by treating with alkyl iodide. The results of the action of methyl iodide admit of an ambiguous interpretation when viewed from the standpoint of Ref.¹ Here, besides the absorption of the amidine by methylene, an addition of hydrogen iodide to the double bond of the amidine may first take place leading to a rearranged product.

In the case of the diazoamido bodies H. Goldschmidt² has employed a reagent for determining the constitution with which the possibility of a rearrangement is excluded, namely, phenyl isocyanate, his leading thought being that, in reactions with phenyl isocyanate, all traces of moisture, acids, etc., can be excluded, which could cause the change of one form of these closely allied "tautomeric" substances into the other. Further, phenyl isocyanate cannot be absorbed by a double bond of the body whose constitution is to be determined; on the contrary, the only possible reaction is an absorption of the latter body by the isocyanate, giving a urea derivative, the determination of whose constitution fixes that of the compound in question. This excellent reagent was applied in the present investigation with the view of deciding between the two possible formulas *a* and *b* (p. 44) for the body $\text{C}_{20}\text{H}_{16}\text{N}_3\text{O}$.

The Action of Phenyl Isocyanate on 2-Phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline.

The substances do not act readily in the cold nor by heating at 150° for one hour. The desired reaction took place, however, when 7 grams of the body $\text{C}_{20}\text{H}_{16}\text{N}_3\text{O}$ were dissolved in 80 cc. of dry benzene containing 2.6 grams of phenyl isocyanate and allowed to stand for eleven days in a well-corked flask placed in a desiccator which was kept in a light place. The solution, which had become somewhat brown, was treated with alcohol to convert the unchanged cyanate into easily soluble urethane, since by exposure to the air the

¹ Ann. Chem. (Liebig), 298, 202.

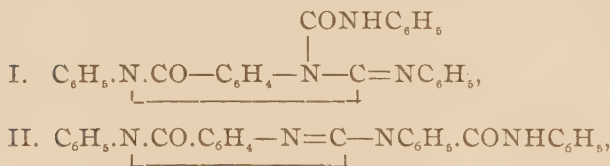
² Ber. d. chem. Ges., 21, 2557.

cyanate would absorb water with the formation of carbanilide, which would be difficult to remove. The benzene was distilled off in a vacuum and the viscous residue dissolved in 60-70 cc. of hot alcohol. From the brown solution a large amount of colorless crystals separated on cooling. These consist of a mixture of the unchanged basic body, $C_{20}H_{15}N_3O$, and the new urea. To remove the former the mixture was treated with dilute hydrochloric acid. The neutral insoluble residue by recrystallization from hot alcohol gave 3.2 grams of colorless needles, melting at 127° . According to its behavior and its analysis, the new substance is the expected urea.

0.1099 gram gave 13.2 cc. N_2 at 23° and 742.2 mm.

	Calculated for $C_{27}H_{20}N_4O_2$.	Found.
N	12.96	13.28

The urea must have either the constitution I. or II.



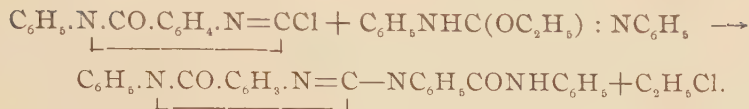
corresponding to the formulas *a* and *b* (page 44) respectively, for the body $C_{20}H_{15}N_3O$.

By heating to 130° the urea is completely decomposed into phenyl isocyanate and the body $C_{20}H_{15}N_3O$. The latter, after removing the cyanate in a current of air, was perfectly pure, and formed a white crystalline mass, having the correct melting-point, 163° . Its identification was established by mixing with the pure substance, when the melting-point remained unchanged.

It was hoped that a urea of constitution II could be prepared by the following method, which would leave no doubt of its constitution, but all attempts were unsuccessful. 2-Chlor-3(N)-phenyl-4-ketodihydroquinazoline and ethylisodiphenylurea¹ should react² to give a body of constitution II:

¹ Lengfeld and Stieglitz: Ber. d. chem. Ges., 27, 926.

² *Vide* paper by Dains soon to be published in The Journal of the American Chemical Society.



The two substances were fused together, but no apparent action took place below 230° ; from 230° to 260° a gas was given off which, by its burning with a green-bordered flame, was identified as ethyl chloride. Oily drops condensed on the walls of the upper portion of the tube; these had the powerful, unmistakable odor of phenyl isocyanate. From the dark residue no urea of the nature expected could be isolated. From the fact that ethyl chloride and isocyanate are formed, it is probable that the reaction takes place in the manner predicted; but the complex urea formed, whether I or II, is unstable at the temperature of the reaction and breaks down into isocyanate and the body $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$, exactly as the urea above described is completely decomposed at 130° , giving just these products. This view is further supported by the fact that ethylisodiphenylurea alone gives no odor of isocyanate when heated; the isocyanate observed in the reaction must therefore come from the decomposition of an unstable urea.

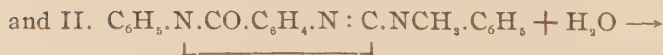
As the pure chloride and urea ether react only far above the decomposition-point of the urea expected, equal molecules of the quinazoline chloride and ethylisodiphenylurea were dissolved in dry benzene and boiled together for twenty hours, but no reaction took place.

These attempts to determine the constitution of the body $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$ having failed, owing to the unusual difficulty with which the chlorine in 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline enters into reaction, recourse was had to von Pechmann's methylation method for distinguishing closely allied amidines. This method, while less reliable, perhaps, led to a definite result, the methyl group going into position 1; in accordance with this the urea just described would have the constitution represented by formula I, p. 46.

The Action of Methyl Iodide on 2-Phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline.

Two grams of the quinazoline and 20 grams of methyl

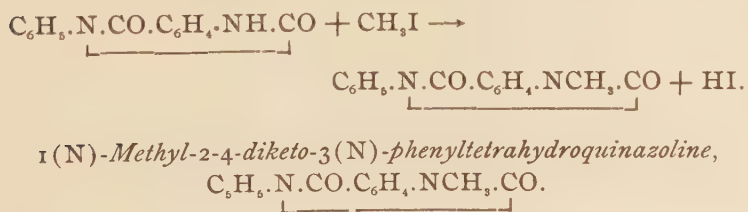
iodide, in which the quinazoline is easily soluble, were heated in a sealed tube to 100° for nine hours. The brown product was partly insoluble in the excess of methyl iodide. The latter was distilled off, and the residue dissolved in pure acetone, in which it is easily soluble. The acetone solution was treated with aqueous hydrochloric acid and much water added. A brick-red tar separated in small quantity, leaving a colorless solution of the bases, which were precipitated fractionally by alkali. After one crystallization from alcohol, the first fraction was the nearly pure unmethylated white base, $C_{20}H_{16}N_3O$, as was shown by its melting-point (162°), which changed to $162^{\circ}.5$ by mixing with some of the pure body, $C_{20}H_{16}N_3O$ (m. p. 163°). The second fractional precipitate with alkali, after one crystallization from alcohol, melted at 135° – 140° , and was evidently a mixture. The third fraction, which was small, after recrystallization from alcohol, melted at 174° . The new body, which was found to be the methyl derivative of the white base, $C_{20}H_{16}N_3O$, forms colorless needles melting at 174° , easily soluble in alcohol. The perfectly pure substance amounted to but 0.05 gram, but the experiment was not repeated to obtain sufficient for an analysis, as the constitution could be firmly established only by the saponification products. The two possible reactions are represented by :



It was finally established that the products of saponification are those given by reaction I.—aniline and 1(N)-methyl-2-4-diketo-3(N)-phenyltetrahydroquinazoline. The base melting at 174° produced by methylation of the white base (m. p. 163°) must therefore be 1(N)-methyl-2-phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline, and the white base itself

(m.p. 163°) is accordingly 2-phenylimido-3(N)-phenyl-4-keto-tetrahydroquinazoline.

The methylated body (m. p 174°) was heated in a sealed tube with concentrated hydrochloric acid to about 180° for four hours. The product consisted of light-colored needles, insoluble in the acid. Water was added and the crystals filtered off. The filtrate gave no precipitate with alkali, showing the saponification to have been complete. The crystals are insoluble in dilute acids and alkalies, somewhat soluble in hot concentrated hydrochloric acid, and crystallize out on cooling. The crude saponification-product melted at 222° , and after dissolving in benzene and precipitating with ligroin (40° – 60°), when the substance was obtained in nearly white needles, the melting-point was 223° . 2-4-Diketo-3(N)-phenyltetrahydroquinazoline, the product to be expected, if equation II, page 48, represented the saponification reaction, melts at 272° and is soluble in alkali. It was therefore thought that the substance melting at 223° must be its 1-methyl derivative, 1(N)-methyl-2-4-diketo-3(N)-phenyltetrahydroquinazoline, the saponification-product to be expected according to equation I. This substance had, however, been prepared by Fortmann¹ from methylanthranilic acid and phenyl isocyanate, and he gives the melting-point at 233° . In all other respects the body obtained by me and melting at 223° showed the behavior of Fortmann's body. To settle the question, raised by this discrepancy in melting-point, I prepared the same substance by methylating 2-4-diketo-3(N)-phenyltetrahydroquinazoline, in alkaline solution, according to



Two grams of 2-4-diketo-3(N)-phenyltetrahydroquinazoline, dissolved in 65 cc. of methyl alcohol, containing 18 cc.

¹ J. prakt. Chem. [2], **55**, 130.

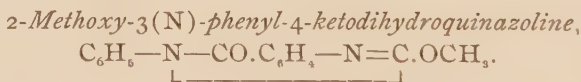
(1 mol.) of $\frac{N}{2}$ -potassic hydrate was boiled with 5 to 6 grams of methyl iodide for one hour. On cooling, colorless needles separated in considerable quantity. The substance was recrystallized from alcohol containing a little aqueous alkali, to remove any unchanged diketone. After two more crystallizations from pure alcohol, colorless needles, melting at 224° , were obtained; neither by further recrystallization from alcohol nor by dissolving in benzene and precipitating with ligroin could the melting-point be raised above 224° . An analysis proved the purity of the substance.

0.2045 gram gave 0.5339 gram CO_2 , and 0.0866 gram H_2O .

	Calculated for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$.	Found.
C	71.43	71.22
H	4.76	4.74

The body is therefore 1(N)-methyl-2-4-diketo-3(N)-phenyl-tetrahydroquinazoline. In all particulars, excepting melting-point, it agrees with that of Fortmann. It is insoluble in both acids and alkalis; it has further the exact properties of the methyl body obtained by the saponification of the methylation-product of the body $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}$. This was very faintly colored, and melted at 223° (instead of 224°), and a mixture with the pure analyzed body melted at 223° - 224° , showing the identity of the two.¹

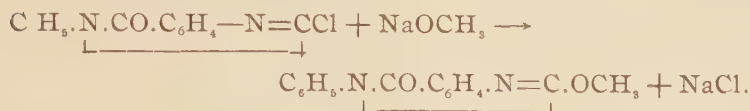
To remove the last possible doubt that the body obtained by methylating 2-4-diketo-3(N)-phenyltetrahydroquinazoline in alkaline solution is really the (N)-methyl derivative and not the oxymethyl ether, 2-methoxy-3(N)-phenyl-4-ketodihydroquinazoline, $\text{C}_6\text{H}_5\text{—N—CO.C}_6\text{H}_4\text{—N=C.OCH}_3$, this latter was prepared.



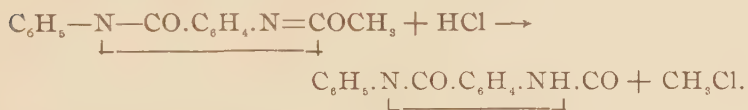
The above oxy-ether was made by heating 2-chlor-3(N)-

¹ I can assign no reason for the difference of 9° between the melting-point of 1(N)-methyl-2-4-diketo-3(N)-phenyltetrahydroquinazoline found by Fortmann and that found by myself. As I obtained the substance by two entirely independent methods, I am inclined to think that the lower melting-point, found by me, is the correct one, and that Fortmann's value may be due to a typographical error, 233° being given for 223° .

phenyl-4-ketodihydroquinazoline with sodium methylate in methyl alcohol, according to



After filtering off the common salt formed and adding a little water, colorless crystals separated, which, after crystallization from methyl alcohol formed, apparently, rhombohedrons melting at 134°. The chloride used melts at 133°, but the new substance contained no chlorine, and a mixture with the chloride showed a strong depression of the melting-point (to about 110°) as expected. The new body dissolves in concentrated hydrochloric acid and, on warming, a gas which burned with a green-bordered flame (methyl chloride) was given off, while a white insoluble crystalline precipitate was formed. The latter dissolved in dilute alkali, with a blue fluorescence, and was undoubtedly 2-4-diketo-3(N)-phenyltetrahydroquinazoline, formed according to the equation :



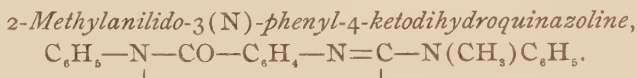
The method of synthesis and the behavior with hydrochloric acid leave no doubt that this new ether (m. p. 134°) is the oxygen ether of 2-4-diketo-3(N)-phenyltetrahydroquinazoline ; the isomeric ether (m. p. 224°) obtained by methylating the diketone in alkaline solution must therefore be the nitrogen ether, 1(N)-methyl-2-4-diketo-3(N)-phenyltetrahydroquinazoline, $\text{C}_6\text{H}_5\cdot\text{N}\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{NCH}_3\cdot\text{CO}$, which is in accord

with the behavior of all analogous alkali salts of acid amides when subjected to methylation. The methoxy derivative was not analyzed.

Since 1(N)-methyl-2-4-diketo-3(N)-phenyltetrahydroquinazoline, together with aniline, is obtained by the saponification of the methylation-product of the body, $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$, as represented by equation I, p. 48, the latter methyl body

(m.p. 174°) must be 1(N)-methyl-2-phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline, $\text{C}_6\text{H}_5\cdot\text{N}\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{NCH}_3\cdot\text{C}=\text{N}\cdot\text{C}_6\text{H}_5$.

The above proof of the constitution of the methyl derivative just discussed was fully confirmed by preparing synthetically the only other isomeric methyl derivative that could possibly be obtained by methylating a base of the constitution *a* or *b* (p. 44); *viz.*, 2-methylanilido-3(N)-phenyl-4-ketodihydroquinazoline.

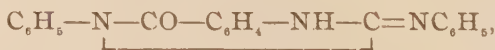


2-Chlor-3(N)-phenyl-4-ketodihydroquinazoline was heated with pure, dry, freshly distilled monomethylaniline to 180° for two hours. The viscous product was treated with hydrochloric acid, in which it dissolved; but very soon a heavy white precipitate, which may have been the hydrochloride of the new base, separated. This was filtered off and dissolved in dilute acid, and precipitated by alkali. By dissolving the free base in methyl alcohol and adding water slowly the body separates in nearly colorless needles, which are very soluble in ethyl and methyl alcohol, less in ether, almost insoluble in low-boiling ligroin, and insoluble in water. The body is a base, being readily soluble in acids and precipitated unchanged by alkalies. For the analysis the body was crystallized from ether by the addition of ligroin, and partial evaporation in a vacuum, and so obtained in colorless needles, melting at 123°.

0.1002 gram gave 11.7 cc. N₂ at 19° and 733.7 mm.

	Calculated for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}$.	Found.
N	12.84	13.24

Not a particle of this low-melting methyl derivative was obtained by treating the white base,



with methyl iodide; the sole methylated derivative was proved to be 1(N)-methyl-2-phenylimido-3(N)-phenyl-4-ketotetra-

hydroquinazoline (m. p. 174°). If the supposition be correct that, by the action of methyl iodide on the body, $C_{20}H_{16}N_3O$, the methyl group has taken the position formerly occupied by the "labile" hydrogen atom, it follows that the body, $C_{20}H_{16}N_3O$, has the constitution (a) page 44. Assuming this to be the case, the body has been named accordingly; though as has been pointed out, this assumption is not yet entirely free from objection, and the possibility that (b), page 44, is by no means absolutely excluded.

The preparation of the two isomeric methyl derivatives of the above base, $C_{20}H_{16}N_3O$, was carried out with the further object of discovering, if possible, whether the remarkable change of color, when the yellow body, $C_{26}H_{20}N_4$, is converted by saponification by acids into the colorless one, $C_{20}H_{16}N_3O$, is due to a shifting of the "labile" hydrogen atom giving rise to the isomeric form. The fact that both of the methyl derivatives of the body, $C_{20}H_{16}N_3O$, are colorless shows that the isomeric form of the original body, if it could exist, would also be colorless; so that the color of the yellow body, $C_{26}H_{20}N_4$, is evidently not due to either possible arrangement of the guanidine group of the molecule. The cause of the color must be intimately connected with the 4-phenylimido group, since when this is removed the body becomes colorless.

Synthesis of 2-4-Phenylimido-3(N)-phenyl-4-ketotetrahydroquinazoline (The Yellow Base, $C_{26}H_{20}N_4$),



One gram of 2-chlor-3(N)-phenyl-4-ketodihydroquinazoline and 0.9 gram of phosphorus pentachloride were dissolved in 5 cc. of phosphorus oxychloride and boiled for ten minutes. No evolution of hydrogen chloride was noted, which was good evidence that chlorination of the benzene rings had not taken place. After distilling off the phosphorus oxychloride the remaining brown oil was mixed directly with about 5 grams of aniline. The reaction took place at once, the mixture became hot, and, on cooling, crystals of aniline hydrochloride separated out. An oil was separated from the crystals by taking up in chloroform and, after removing the solvent, the

oil was boiled for ten minutes with more aniline. On distilling off the aniline, a dark-colored, viscous mass remained. This distilled in a vacuum, with apparently little decomposition, giving a solid yellow distillate, which was dissolved in benzene and the latter partly evaporated. Upon the addition of alcohol a small amount of the characteristic yellow prismatic needles of 2-4-diphenylimido-3(N)-phenyltetrahydroquinazoline ($C_{26}H_{20}N_4$) soon separated out. After recrystallization from alcohol the needles were almost pure and showed the melting-point 170° – 171° (instead of 171°). On cooling, the substance crystallized in the melting-tube, and on reheating melted at 182° – 183° (instead of 184°), showing thus the exact behavior of the yellow body, $C_{26}H_{20}N_4$, obtained from carbodiphenylimide.

An addition of the α -form (prisms, melting-point 171°) of the body obtained from carbodiphenylimide to the substance made synthetically, did not change the melting-point.

It was of great interest to determine, if possible, the cause of the difference between the α - and β -forms of the yellow body $C_{26}H_{20}N_4$. When it was found, from a solution of either of the two forms, that one was obtained which was the less soluble in the solvent used,¹ it was thought that the two forms must be physical or crystallographic modifications of the same substance, and consequently identical in solution, and thus show in solution the same chemical behavior. In endeavoring to determine the position of the hydrogen atom in the yellow bases (*a* and *b*, p. 26) by converting into the urea by means of phenyl isocyanate, and saponifying to the white urea whose constitution has been fairly well established by the methylation process just discussed, the surprising discovery was made that the α - and β -forms do not seem to act alike in solution. This discovery has been made so recently that the investigation has not been completed, but the point seems so interesting that a brief statement of the facts thus far established will be made now.

The Action of Phenyl Isocyanate on the Yellow Bases, $C_{26}H_{20}N_4$.

The substances react with great difficulty if cold, and heat-

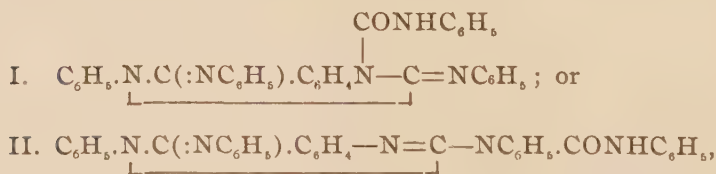
¹ *Vide* p. 33.

ing is not effective, as was the case in the formation of the urea of the body $C_{26}H_{16}N_3O$. To accomplish the reaction I proceeded as follows: 2 grams of the α -form (m. p. 171°) of the body, $C_{26}H_{20}N_4$, and 1.3 grams of phenyl isocyanate (about double the calculated amount) were dissolved in 100 cc. of pure dry benzene, which was much more than enough to prevent the separation of any of the β -form, and the solution allowed to stand in a well-stoppered bottle, exposed to as much sunlight as possible, for three weeks. At the end of this time the solution remained clear and no crystals had separated. The solution was treated with 1 cc. of alcohol, to destroy the excess of cyanate, and most of the benzene distilled off in a vacuum, the temperature being kept below 24° . The concentrated solution thus obtained gave, with alcohol, a precipitate of perhaps a gram of the nearly pure unchanged body, $C_{26}H_{20}N_4$, melting at 170° , instead of 171° . The mother-liquor, on further evaporation in a vacuum at not over 24° , gave a quantity of light-yellow crystals, which melt at 80° – 90° , and on heating give off phenyl isocyanate. The crystals so obtained are a mixture of the original base, $C_{26}H_{20}N_4$, and the corresponding urea; these were separated by treating with sufficient acetone to dissolve the urea, which is very easily soluble, and leave most of the other body. The acetone solution, on addition of alcohol, gave a crystalline precipitate, which, after dissolving again in acetone and precipitating with alcohol, yielded 0.45 gram of light-yellow diamond-shaped plates. The body, after drying over night in a desiccator, melts at 80° – 90° with the evolution of a gas (but no darkening), and by gently heating on a platinum foil gives off much cyanate (recognized by the odor).

A determination of the molecular weight by the freezing-point method in benzene, using 0.43 gram of the substance which had been dried in a vacuum-desiccator over night, gave the value 239 instead of 507, as calculated for the urea, $C_{38}H_{25}N_6O$. The low result indicated a dissociation of the urea into two molecules; but that phenyl isocyanate does not split off in the benzene solution is shown by the fact that the urea was recovered unchanged from the above benzene solu-

tion, after partial evaporation of the solvent, by the addition of alcohol, which, if free cyanate had been present, would have united with it forming a urethane. The additional fact, already mentioned, that a gas was given off on melting at 80° – 90° , indicated the presence of some of the solvent, alcohol or acetone, from which the body was crystallized. An experiment seemed to confirm this. A portion of the pure-recovered urea, after drying over night in a vacuum, as before, weighed 0.3664 gram. On keeping in a good vacuum over sulphuric acid, the substance lost weight gradually for a period of ten days, when the weight was 0.3303 gram. The loss amounts to 1.2 molecules of alcohol to one of the urea. The dry urea now melted at 84° – 86° without evolution of a gas.

The larger part of the above urea was lost in an attempted analysis in which the tube broke. That the new body was really the urea was shown, however, by heating 0.05 gram, contained in a test-tube, to 120° – 130° in a bath; much cyanate was given off, and this was removed by a current of air. After a few minutes, when the odor of the cyanate had entirely disappeared, the residue solidified, at the temperature of the bath, to a yellow crystalline mass; this upon dissolving in a mixture of boiling acetone and alcohol and adding a few drops of water crystallized in the characteristic yellow prisms of the α -form of the body $C_{26}H_{20}N_4$. The pure dry crystals so obtained weighed 0.026 gram (theory requires 0.038) and melted at 171° ; on cooling, the substance solidified, and on reheating melted at 184° . The above crystals (m. p. 171°) mixed with the pure α -form of the body, showed no change of melting-point. The urea is therefore to be represented by one of the following two formulas:



corresponding to the formulas *a* and *b* (p. 136), respectively,

for the body $C_{26}H_{20}N_4$. The ease with which the body decomposes makes it very difficult to carry out any reaction which would discriminate between the two formulas and no solution of the problem has yet been reached.

The β -form of the body, $C_{26}H_{20}N_4$, *does not react with phenyl isocyanate*, except to a very slight extent. The experiment was carried out twice in exactly the same manner, and at the same time as that with the α -form, the same quantity of substance being used. The product treated as before yielded only a very small amount (perhaps 0.05 gram) of a body which was apparently identical with the urea obtained from the α -form, but the larger part, by far, was the unchanged material.

The difference in behavior towards phenyl isocyanate would seem to show that the two forms of the body, $C_{26}H_{20}N_4$, are not identical *in solution*, as would be the case if they were simply physical modifications of the same chemical individual. However, this point cannot yet be considered as settled, and investigation will be continued in this direction.

In conclusion I wish to express my sincere thanks to Dr. Julius Stieglitz, under whose supervision the above investigation has been pursued, for the personal interest he has taken in the work, and for the valuable assistance and instruction received at his hands.

